American Journal of Obstetrics and Gynecology

VOL. 31 APRIL, 1936 No. 4

Original Communications

THE PROBABLE RÔLE OF THE HYPERCHOLESTEREMIA OF PREGNANCY IN PRODUCING VASCULAR CHANGES IN THE PLACENTA, PREDISPOSING TO PLACENTAL INFARCTION AND ECLAMPSIA*

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ON THE basis of a careful gross and microscopic study of the lesions found in a series of more than one thousand placentas, correlating the clinical and pathologic findings, and producing the clinical and pathologic evidences of eclampsia by the injection of placental autolysate into guinea pigs, we stated our belief[1] that eclampsia is the result of absorption into the maternal blood of the split products of placental protein from an acutely infarcted area, and in another communication[2] described a possible mode of origin of the principal poisons, guanidine and histamine, from placental arginine and histidine. Since the publication of these articles, further careful study of placentas from both normal and toxic patients has only served to confirm our belief in the correctness of this theory.

Notwithstanding the consistency with which acute infarcts may be observed in the placentas of patients affected by preeclampsia, eclampsia, and abruptio placentae, statements continue to appear in the literature denying the occurrence of such a relation. Failure to appreciate this relation is due, mainly, to examining the placenta in the fresh state and

*Read before the Fulton County Medical Society, September 19, 1935.

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to limiting the search for infarction to merely a surface inspection of the placenta. The infarcts are best demonstrated by fixing the entire placenta, stripped of its membranes and adherent blood, in 10 per cent formalin solution for two weeks and then examining by cutting it in strips of not more than 1 cm. in thickness.

Infarcts of slow development are white, sharply outlined, firm, and are usually found on the margin of the placenta (Fig. 14).[1] This type of infarct is never responsible for toxemia of pregnancy.

Infarcts of rapid development, first described by Young[3] in 1914 appear as dark areas having a homogeneous, fused, melted appearance, in distinct contrast to the surrounding lighter colored, spongy normal placental tissue (Figs. 6 and 10).[1] A more detailed description of the microscopic appearance, and the correlation of the pathology and the toxic effects, of the more acute types of infarcts have been recorded in our first communication,[1] to which the reader is referred.

At the time of our first study on the relation of placental infarcts to eclampsia, the frequent finding of obliterative endarteritis indicated that this process was apparently responsible for the occurrence of the nontoxic firm white infarcts so frequently found in mature placentas. This, however, did not adequately explain the evidences of sudden extravasations of blood which appear so frequently as small collections of yellow fibrin beneath the amnion on the fetal surface of the placenta, or in massive form, as shown in Fig. 5;[1] neither did it satisfactorily explain the fresh or recent extravasations of considerable size, in the substance of the placenta as shown in Fig. 10.[1] Young[3] considered these areas of hemorrhage to be due to disturbances in the maternal circulation at the placental site, but in view of the sinuslike circulation at the placental site and the unusually free communication between the villi, it is difficult to explain their origin in this way.

To one of us (R. A. B.)[1] it seemed not only reasonable but probable that the impact of vigorous fetal movements on the exposed vessels on the surface of the placenta accounted for the evidence of thrombosis or rupture of the vessel at the site of trauma, with resulting infarction of the dependent placental tissue.

While the factor of trauma seemed to be the exciting cause of thrombosis or rupture of the fetal arteries, the tendency to obliterative endarteritis remained unexplained and did not seem to be entirely adequate as a predisposing cause of the thrombosis or rupture following trauma. Furthermore, it seemed difficult to explain the rare but occasional occurrence of eclampsia at the fourth or fifth month of pregnancy when the fetal movements are obviously only mild.

Throughout the entire period of study of placental infarcts, one of us (R. A. B.) has been impressed, not only with the tendency to obliterative endarteritis, but also with an occasional peculiar irregular thickening and bulging of the inner layer of the placental arteries, apparently

due to a swollen vacuolated condition of the cells within the intima, causing the lumen to appear distorted, excentric, slitlike, or almost obliterated (Figs. 1 and 2).

The significance of this appearance was not appreciated until a study of Timothy Leary's work[4] on cholesterol-induced changes in the coronary

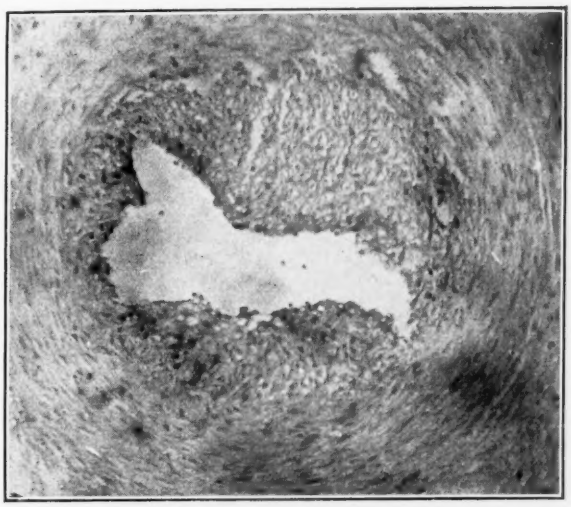

Fig. 1.—Section of placental artery on fetal surface of placenta from case of abruptio placentae. Appearance is that of more advanced cholesterol vascular change, with excentric narrowing of lumen due to increased fibrosis and accumulation of lipoid cells beneath endothelium.

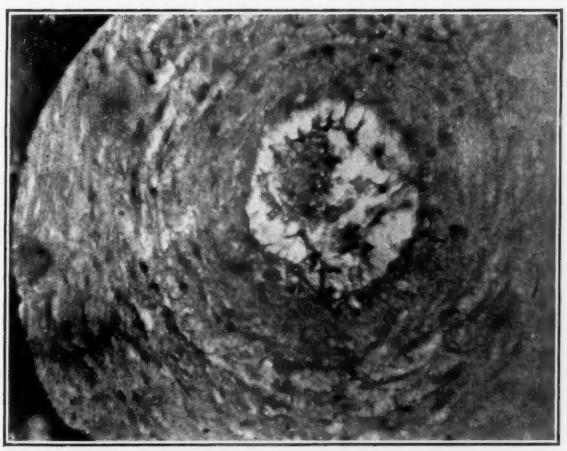

Fig. 2.—Section of placental artery from villous stem of medium size showing lipoid cells beneath endothelium. Appearance is that of early cholesterol vascular change.

arteries of rabbits strongly suggested that the unusual appearance of the placental arteries was probably of the same nature and origin. Leary, in necropsies upon individuals dying suddenly, apparently from heart failure, demonstrated cholesterol-like changes within the intima of the

coronary arteries, which apparently had so altered the lining and caliber of the vessels as to induce thrombosis, followed by infarction and sudden cardiac death (Fig. 3). Since the appearance shown in Fig. 4 is apparently specific for vascular changes produced by cholesterol, the

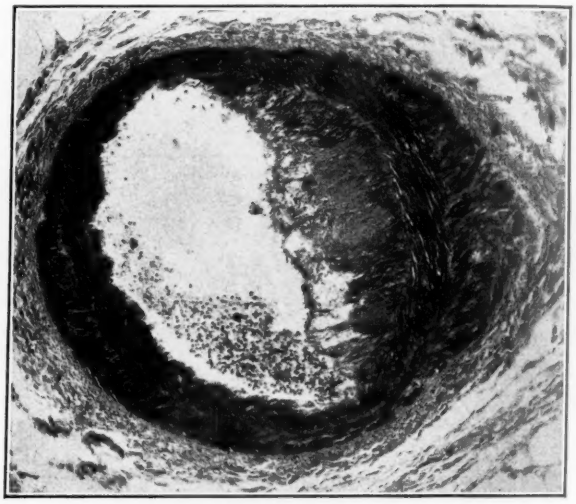

Fig. 3.—"Human coronary artery in Case 3; ×130; fibrosis replacing lipoid cells." Leary,[4] Fig. 13-B.

Fig. 4.—"Aorta with left coronary artery of rabbit; ×65." Leary,[4] Fig. 22.

similarity in appearance of the changes in the human coronary (Fig. 3), and in the placental arteries (Figs. 1 and 2) indicates a cholesterol effect, which in the latter, readily explains a tendency to thrombosis occurring spontaneously or as the result of trauma of fetal movements, with resulting placental infarction and toxemia.

The hypercholesteremia of pregnancy was first demonstrated by Hermann and Neumann[5] in 1912. It has long been noted that the great majority of cases of gallstones occur in women who have borne children. Shiskin[6] observed that the increase in cholesterol began as early as the second or third month of pregnancy, and continued until some time after delivery. Taking the normal range of cholesterol as 140 to 170 mg. per 100 c.c. of whole blood, with an average of 153.7 mg., as reported by Oser and Karr,[7] these authors found an average value of 186.8 mg. in twenty-one cases of full-term normal pregnancy. Ferguson and Priestley[8] collected blood from thirty patients at term and on the second, seventh, and twelfth days after delivery, also at monthly intervals thereafter and found an average value of 221.3 mg. at term. The values in multiple pregnancy were considerably above the average. They observed that the cholesterol values often remained high for some months after delivery. It has been observed[5] that the hypercholesteremia of pregnancy passes off more quickly in women who nurse their babies.

Cholesterol, a constituent of every animal cell, is a relatively insoluble substance of complex formula, $C_{27}H_{45}OH$, of colloid nature, and highly resistant to enzyme action. It exists in the blood as cholesterol and cholesterol esters, in nearly equal proportion, the latter resulting from union with fatty acids. According to Schoenheimer (quoted by Leary) cholesterol and viosterol are the only sterols which are absorbable. Herbivora are able to synthesize cholesterol, but the principal source of this substance, in the human being, is from the ingestion of such products as eggs, butter, cheese, milk, fried foods, liver, kidneys, oily fish, brain, soy bean, and pork fat. According to Gulli-Lindh Muller[9] it is thought that the synthesis of cholesterol takes place in the entire reticuloendothelial system. An increase in blood cholesterol can be obtained by a diet rich in cholesterol-containing foods, especially when combined with some oily vehicle. Conversely, it can be lowered by a diet poor in such foods. Starling regards it as the framework or skeleton of the cell structure.

It seems reasonable, therefore, that at the onset of pregnancy there should be some mechanism whereby the mobilization of cholesterol might be effected, to supply the needs of the rapidly growing fetus. Moehlig and Ainslee[10] injected rabbits with 1 c.c. of pituitary extract daily for ten days and found an increase in the blood cholesterol of 30 per cent in 85 per cent of the rabbits, and 14 per cent in 10 per cent of the rabbits. There was no change in 4 per cent of the rabbits.

According to Fluhmann,[11] Chauffard and his coworkers of the French School hold that cholesterol is actually manufactured by the cortex of the adrenals, aided by the corpus luteum, particularly in its retrogressive phase. The fact that Shiskin and Okey and Boyden found the blood cholesterol increased at the end of each menstruation, would seem to support this theory. Furthermore, Patrzek and Quinquaud found more cholesterol in the suprarenal vein than in the blood from other vessels. The German school holds that the suprarenals merely act as depositories and not as manufacturers of cholesterol. It is stated that

hypo- and hyperplasia of the pituitary gland are accompanied by hypo- and hyperplasia of the suprarenal cortex and that anencephalic fetuses show hypoplasia of the suprarenal cortex.

It is probable that under the influence of increased activity of the pituitary gland, which occurs early in pregnancy, there is a stimulation of cholesterol metabolism to care for the needs of the rapidly growing fetus. There is likewise some stimulation of thyroid activity in pregnancy, which would tend to lower the blood cholesterol, but this is evidently not sufficient to prevent the occurrence of hypercholesteremia. However, in hypothyroid states the cholesterol value is markedly increased. By way of speculation, it is possible, therefore, through overactivity of the pituitary and underactivity of the thyroid, that in certain pregnant patients, an overmobilization of cholesterol may take place. It may also be increased by an overingestion of cholesterol-containing foods.

McMeans[12] states that if hypercholesteremia reaches a certain degree, there results a secretion of an excess of cholesterol in the bile predisposing to gallstones, and a storage of cholesterol in the entire reticuloendothelial system, but principally in the liver and suprarenal cortex, corpus luteum and to some extent in the spleen.

He states that the intima of the aorta and pulmonary artery, as well as the endothelium of the smaller arteries and arterioles in rabbits, shows proliferation of the lining cells and storage of cholesterol following cholesterol feeding. Rothschild found that the liver seemed to play a very important part in preventing excessive hypercholesteremia, by secreting an increased amount of cholesterol in the bile. According to Aschoff and Landau, the endothelial tissue of the spleen, lymph nodes, and bone marrow, together with the adrenal and Kupfer cells of the liver, constitute an important intermediary apparatus in cholesterol metabolism. To quote McMeans, "as the amount of cholesterol gradually increases within the body, the demand for greater assistance in caring for the material becomes imperative. The liver and adrenals comprise the most important organs first called on. When the work becomes too heavy for them, they are assisted by the corpora lutea, the spleen and the endothelium of the blood vessels." Pierce, McNee and Grigaut observed a marked increase of cholesterol in the bile during the hypercholesteremia of pregnancy.

According to Slemons and Stander,[13] the fats and lipoids in the blood are approximately 900 mg. per 100 c.c. during the latter part of pregnancy, a value which is approximately one-third greater than normal. This may be of significance in the metabolism of cholesterol, the solubility and absorption of which is facilitated by combination with fat. They estimate the total cholesterol in the maternal blood as 200 to 250 mg., half of which is free and the other half cholesterol esters. The total cholesterol in the fetal blood varies from 120 to 200 mg., nearly all of which is free cholesterol, as the cholesterol esters do not seem to be able to pass through the placenta. Chauffard found the cholesterol in the blood of the umbilical vein much higher than in that from the umbilical arteries, which apparently indicates that the fetus obtains cholesterol from the mother.

Klotz[14] studied the vascular changes induced by the intravenous injection of 0.5 to 2 c.c. of 1-15 cholesterol in oleic acid two to three times a week into young rabbits at intervals of six days to three months. During the first few weeks the fat alone was visible in the capillaries or in the vacuoles of large phagocytic cells. Later the cholesterol crystals separated from the oil globules and became embedded in the large foreign body phagocytes around which developed a marked proliferative

lesion. He was of the opinion that the cholesterol crystals were separated from the oil droplets by intracellular lipolysis. The endothelial cells proliferated and enlarged greatly when phagocyting these large oil masses and the nucleus was often displaced and flattened. The proliferative changes in the larger vessels led to an irregular thickening along one border of the lining, simulating the appearance of early endarteritis or thromboangiitis obliterans. A tortuous course of the vessel predisposed to localized proliferation and obliterative change. Wherever the introduced fatty material was in direct contact with the vessel wall, either by adherence or plugging, a localized proliferation resulted. The lung capillaries showed a greater frequency of cholesterol change, next to this the kidney, heart, and spleen. There was almost uniform splitting of the internal elastic lamina into multiple layers, but very little change in the media. Calcification occurred later. Fats alone are incapable of producing the proliferative change.

Duff[15] states that the foam cells which accumulate within the intima in experimental cholesterol arteriosclerosis are almost certainly macrophages and resemble the large mononuclear phagocytes. The collections of cells form the yellow plaques which appear as the first lesions in the lining of the artery. Contrary to Klotz' opinion, he holds that the endothelium is apparently passive. Crystals of fusiform lipoid material, resembling cholesterol, may be seen in the foam cells and in the intercellular ground substance. In experimental cholesterol feeding, twenty-five days are required for recognizable changes to appear. The lesions appeared earlier when the cholesterol was given in an oily or fat medium than when it was given dry. Apparently the fat aids in absorption partly in a physicochemical way and also by forming esters. *Experimental damage to the vessel wall through manipulations or slight cauterizations of the adventitial surface induced a much more abundant deposit of lipoids at the site of injury in the media of the artery and in a much shorter time, the lesion being recognizable in nine to fourteen days. It was found that lipoid deposits did not occur in other undamaged portions of the artery even with considerable hypercholesteremia, but did occur in the damaged portions even with slight hypercholesteremia.*

In order to determine the character and degree of vascular change taking place during pregnancy, studies were made on placentas obtained from normal, preeclamptic, abruptio and eclamptic cases as to the character of the infarcts and supplemented by the usual clinical and laboratory investigations.

There were four eclamptic patients, three severe preeclamptic patients, and one case of abruptio placentae, all of whom were from the colored service of Grady Hospital. The cholesterol values in these cases varied from 200 to 266 mg., except in one case, a preeclamptic, whose value was 141 mg. The average cholesterol value was 212 mg. Albumin, casts, and high blood pressure were present in all. Fundus examination was done in seven cases and showed moderate to well-marked arterial spasms. Examination of the placentas showed one or more dark to light brown acute infarcts in all cases, which on microscopic examination showed necrotic or disintegrating villi with open intervillous circulation.

There were six mild preeclamptic patients, all of whom were white women and private patients. The cholesterol values in these cases varied from 174 mg. to 241 mg., the average value being 204 mg. One of these, a case of twins, showed a value of 222 mg. There was mod-

erate elevation of blood pressure and albuminuria, and in all but one case, fundus examination showed arterial spasms. The placentas showed one or more small to medium-sized dark to brown red acute infarcts, except in one case in which the examination was apparently negative.

There were twelve normal patients, all of whom were white and private patients. The cholesterol values in these cases varied from 154 mg. to 216 mg., the average value being 191 mg. The placentas showed no infarcts of the acute or subacute type. The cholesterol values in all the white patients, both mild preeclamptic patients and normal cases, were later discovered to be about 20 per cent too low, due to an error in the standard used in the test. The fact remains, however, that in practically all cases, the cholesterol values in pregnancy are much higher than normal, but that the degree of hypercholesteremia does not necessarily indicate the measure of susceptibility to vascular change and toxemia.

A study of the placental vessels from the above cases, and also a review of numerous slides from placental tissues previously studied, showed that cholesterol changes in the vessel wall occurred mainly in the arteries of the medium-sized villous stems, less frequently in the large arteries of the main stems, and very seldom in the vessels or capillaries of the terminal villi. It was also apparent that the characteristic change occurred only here and there in certain vessels and that the majority of the arteries were not affected. The cholesterol-like changes in the placental arteries are well shown in Figs. 1 and 2 and are seen to be of the same character as those found in human coronary thrombosis (Fig. 3) and in the artificially produced cholesterol changes in the coronaries of rabbits (Fig. 4).

There was no change in the veins comparable to that seen in the arteries as localized collections of lipoid cells, but in some veins, scattered lipoid cells were seen in the media or beneath the endothelium. Furthermore, the impression seemed justified that the frequency and degree of the cholesterol vascular change were more marked in eclamptic, preeclamptic, and abruptio patients and less marked in the mild toxemic and normal patients. Further study will be necessary to settle this point. Especial interest centered upon the possible finding of cholesterol crystals in areas where the vessel wall showed cholesterol change with some disintegration, but it could not be determined whether certain suggestive outlines were artifacts or crystals.

Close examination of the lining of the vessel at the site of the lesion indicated that the endothelial cells had apparently preserved a normal intact flattened layer, beneath which the subendothelial cells had proliferated, enlarged, and become lipoid in character. In some arteries, extravasation of red blood cells had occurred into the vessel wall, due to a break in the lining of the vessel. *The distortion and narrowing of the lumen and the tendency to roughening and breaking down of the*

lining of the vessels offer conditions ideal for spontaneous thrombosis and placental infarction, just as occurs in human coronary thrombosis and cardiac infarction with identical vascular changes.

Although Slemons and Curtis[16] did not find hypercholesteremia constantly present in eclampsia, the fact that hypercholesteremia is present in the great majority of pregnancies and that vascular injury induces cholesterol change even with slight hypercholesteremia; the consistency with which cholesterol-like changes may be demonstrated in placental arteries; the marked predisposition to thrombosis or rupture which such vascular changes produce, either spontaneously or excited by the trauma of fetal movements; and the consistency with which acute infarcts may be demonstrated in preeclampsia, eclampsia, and abruptio placentae, afford exceedingly strong evidence that toxemia of pregnancy is a disease of placental autolysis, the basis of which is laid early in pregnancy by the hypercholesteremia of pregnancy.

Furthermore, the fundamental factor of hypercholesteremia may explain many hitherto puzzling facts. According to Gulli-Lindh Muller[9] blood cholesterol is increased by a diet rich in cholesterol-containing foods, especially when combined with some oily vehicle, and, conversely, is lowered by a diet poor in these foods. Studies on blood cholesterol in the Dutch Indies show values far below those obtained in countries where animal products constitute the main part of the diet. May this not explain the low incidence of eclampsia in the tropics? Rosenthal and Patrzek[17] found that hypocholesteremia accompanied the undernourishment during the war. The diet in Germany during the war was greatly deficient in fats and cholesterol-containing foods, and the low incidence of eclampsia in Germany during these years may well have been due mainly to this factor. Overweight people have been found to show hypercholesteremia.

A possible relation of certain other facts and symptoms of pregnancy occurs to one, on the basis of the hypercholesteremia of pregnancy. May it not be that the tendency to brain hemorrhage and the occasional occurrence of edema of the lungs in eclampsia, are favored by cholesterol-induced vascular changes in these organs, leading to weakening of the vessel walls, the actual rupture being due to the damaging effects of histamine? In studying the subsequent pregnancies of patients who have once had severe toxemia or eclampsia, the fact has been established that the incidence of toxemia or eclampsia is increased 25 per cent or more and that it lays the basis for cardiovascular renal disease which greatly shortens the expectancy of life.[18] It is probable that the predisposition to toxemia of pregnancy in certain individuals is based on a hypercholesteremia both during and between pregnancies, according to the individual's diet, hyperpituitarism, or hypothyroidism, as high cholesterol values have been found to persist for many months after pregnancy.[8]

In a recent article Priscilla White[19] states: "The background of diabetes appears favorable to the development of toxemia and eclampsia, the incidence of eclampsia being 5 per cent, compared with an average of 0.3 per cent in a non-diabetic series. The demonstration of excessive prolan in the urine and blood of patients with toxemia (by Smith and Smith) and the excess of toxemias and eclampsias in our own series of cases, gives us a new lead in the search for the lethal factor active the last four weeks of diabetic pregnancies."

The probable interpretation of these facts is that the hypercholesteremia in diabetic patients produces excessive cholesterol changes in the placental arteries which are thereby made more susceptible to thrombosis, occurring spontaneously or secondary to the trauma of fetal movements on the exposed placental arteries. Placental infarction, autolysis, and toxemia, therefore, occur more frequently and extensively in diabetic patients, and the increased prolan in toxemia is probably due to overstimulation of the pituitary resulting from a pathologic amount of necrosis in the placenta. The increased incidence of stillbirths among diabetic patients is more likely the result of decreased caliber or obliteration of the placental arteries from fibrous change following cholesterol changes rather than from a possible toxic effect of the increased amount of prolan. Calcification of the placenta is generally marked in these cases as might be anticipated in tissues of low vitality following atheromatous and fibrous change. It is very probable that unexplained cases of fetal death at or beyond term, in the absence of recognized syphilis, diabetes, or kidney disease, are due to the effect of hypercholesteremia on the placental vessels.

It is the belief of one of us (R. A. B.) that nausea and vomiting of pregnancy may be related to an increased secretion of cholesterol in the bile early in pregnancy until storage of the excess of this substance can take place throughout the body. In a communication from Flipse,[21] he states that the administration of cholesterol and iron in the treatment of patients for anemia is often interfered with by the nausea which is produced. According to experimental work, this storage of cholesterol takes place first in the liver, then in the adrenals, corpus luteum, spleen, and finally in the entire reticuloendothelial system, being most marked in the arteries of the lungs and kidneys. If the liver is forced to store an excessive amount of cholesterol, excessive fatty change occurs in the peripheral portion of the lobule, followed by central necrosis and disintegration of the liver cells of the inner zone, which are the most typical changes seen in fatal cases of pernicious nausea and vomiting of pregnancy. The section of liver shown in Fig. 5 was obtained from a patient who died from pernicious nausea and vomiting during the fourth month of pregnancy. Sufficient work has not been done, as yet, on this type of toxemia to verify this hypothesis.

On this basis, the authors' conception of the toxemias of pregnancy is that of a series of toxic manifestations, fundamentally due to the hypercholesteremia of pregnancy. The sequence of events is probably

as follows: Early in pregnancy the placental hormone stimulates the pituitary gland which apparently controls cholesterol metabolism. The resulting hypercholesteremia may be further increased if there is an associated hypothyroidism or if the diet contains an unusual amount of cholesterol-containing foods. Secretion of some of the excess cholesterol through the bile probably produces nausea and vomiting of pregnancy. By the third or fourth month of pregnancy, the process of storage of cholesterol is probably well under way. The resulting diminution in secretion of cholesterol through the bile brings about relief from nausea and vomiting. If there is excessive storage in the liver, excessive fatty change in the outer zone and even necrosis and disintegration in the cells of the inner zone of the lobules take place. If the amount of cholesterol secretion through the bile, or storage in the liver is not of sufficient degree to cause excessive or possibly pernicious vomiting of preg-

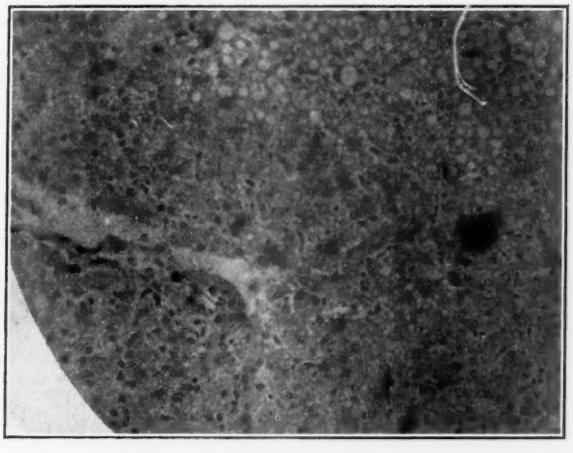

Fig. 5.—Section of liver from case of pernicious vomiting, showing marked fatty infiltration in mid and outer zones of liver lobule. Appearance is that of cholesterol lipoid change.

nancy, the slow-developing cholesterol-induced change in the placental arteries, lays the basis for toxemia of the later months of pregnancy, through the liability to placental infarction, occurring either spontaneously or from the trauma of fetal movements on the unprotected vessels, causing thrombosis or even sudden rupture, followed by acute infarction and autolysis of the affected placental tissue. The poisonous protein split products, mainly peptone, guanidine, and histamine, diffuse into the maternal circulation causing preeclampsia, eclampsia, or abruptio placentae, depending on the rapidity of autolysis and the location and actual amount of infarcted tissue. It is probable that certain pathologic changes in other organs, particularly the kidneys, brain, and lungs, so often associated with toxemia, are predisposed to by cholesterol-induced vascular changes in these organs. It would certainly seem that the so-called deficiency of the liver which exists throughout preg-

nancy even in otherwise normal patients, is probably based upon an excessive degree of fatty change in the outer zone of the liver lobules, which tends to obstruct the fine bile capillaries and ducts.

A satisfactory classification of the toxemias of pregnancy has hitherto been impossible on account of uncertainty as to the nature or source of the poisons. On the basis of our conception of the effects produced by hypercholesteremia at the various stages of pregnancy, the following classification of the toxemias of pregnancy is proposed:

TOXEMIAS OF PREGNANCY

(Fundamentally due to hypercholesteremia of pregnancy)

A. First Half of Pregnancy:

(1) Normal nausea and vomiting of pregnancy:
(Probably due to excessive cholesterol secretion through the bile.)

(2) Pernicious nausea and vomiting of pregnancy:
(Probably due to excessive secretion of cholesterol through the bile plus excessive storage of cholesterol in the liver, producing fatty change and necrosis in the lobules.)

B. Second Half of Pregnancy:

(3) Preeclampsia:
(Due to placental infarction and autolysis, induced by spontaneous or traumatic thrombosis or rupture in placental artery, predisposed to by cholesterol-induced vascular change.)

(4) Eclampsia:
(End-result of 3, dependent on the rapidity and mass of infarction; guanidine effect probably predominating. Infarct usually situated in substance of placenta and of dark to brown red color.)

(5) Abruptio placentae:
(End-results of 3, dependent on rapidity and mass of infarction; histamine effect probably predominating. Infarct usually situated on surface and of brown or brick-red color.)

The so-called nephritic toxemia is not included in the above classification, inasmuch as it is not, per se, a true pregnancy toxemia, but may predispose to or be associated with preeclampsia, eclampsia, and abruptio placentae through an increased tendency to hypercholesteremia. Likewise the so-called "low reserve kidney" is not included since the various degrees of mild or temporary albuminuria or hypertension are due either to the infarction's being subacute or chronic or to the fact that there is a very limited amount of tissue involved.

While the above theory of the etiology of toxemia, as applied to the first half of pregnancy, is admittedly hypothetical, it is supported by very suggestive evidence and is proposed as a promising line of investigation for further research. When applied to the latter half of pregnancy, it furnishes a basis for the clinical and pathologic manifestations and explains many hitherto puzzling facts. To one who will routinely prepare and examine placentas, there will be impressed upon

him certain indisputable facts upon which the theory rests. Placentas from patients free from toxemia do not show the acute type of infarct. Placentas from patients affected with preeclampsia, eclampsia, and abruptio placentae rarely fail to show recognizable areas of acute infarction, if prepared and sectioned in the proper manner. The size of the infarcted area bears a definite relation to the severity of the toxemia, modified to some extent by the acuteness of the process. The location of the infarct determines to a considerable extent whether the toxemia will be manifest as eclampsia or abruptio placentae. The manifestations of eclampsia, both clinical and pathologic, can be produced by injecting autolysate of placental tissue into guinea pigs. The consistency with which hypercholesteremia occurs in pregnancy and cholesterol-like changes can be demonstrated in the placental arteries, furnishes a definite predisposing cause of thrombosis or rupture of the placental arteries. The trauma of fetal movements acts as the exciting cause.

Recognizing the fact that the artificial production of eclampsia by inducing placental infarction through blocking the circulation in a placental artery would establish beyond doubt that eclampsia is a disease of placental autolysis, one of us (R. A. B.), working with Dr. E. D. Colvin, attempted to produce infarction in the placentas of pregnant bitches and rabbits by injections of a small amount of hot oil or saline solution, hoping that an artery crossing the injected area might be thrombosed, and cause infarction and autolysis beyond the injected area. Convulsions occurred in a bitch, during labor, several days after injection, but in the majority of cases, the animal aborted within one to two days, before toxemia could develop.

According to Page and Bernhard[20] and Duff,[15] the administration of iodine or thyroid extract, along with cholesterol, will prevent the characteristic vascular changes in the coronary arteries in rabbits. This suggests the possibility of therapeutic use of iodine or thyroid extract, especially during the last half of pregnancy, to prevent excessive cholesterol storage in the placental arteries. It also suggests a more practical application of basal metabolism determinations in pregnancy. Furthermore, it would seem advisable to restrict fats and cholesterol-containing foods in pregnancy.

As progress is made toward a better understanding of the cause, nature, and effects of the hypercholesteremia of pregnancy, there will no doubt develop a better understanding of the fundamental cause of hypertension in general, and the causes which lead to arteriosclerosis and cardiovascular renal disease.

CONCLUSIONS

1. The hypercholesteremia of pregnancy is probably a normal physiologic response to meet the requirements of rapid cell growth in the fetus and prepare for lactation.

2. An excessive degree of hypercholesteremia of pregnancy is probably due to hyperpituitary or hypothyroid activity and is further increased by a diet high in cholesterol-containing foods.

3. Hypercholesteremia is probably the fundamental basis for the toxemias of pregnancy.

4. It probably is responsible for nausea and vomiting of pregnancy, through an increased secretion into the bile until storage of this material can take place in the reticuloendothelial system.

5. Excessive storage in the liver in the first half of pregnancy is probably the cause of excessive fatty change in the periphery of the liver lobules with subsequent central necrosis in the inner zone of the lobules, which is so consistently found in fatal cases of pernicious vomiting of pregnancy.

6. Excessive storage in the placental arteries with resulting vascular changes is the predisposing cause of infarction in the placenta.

7. Thrombosis or rupture of a placental artery, occurring either spontaneously or produced by the trauma of fetal movements is the exciting cause of acute infarction in the placenta.

8. Acute or subacute infarction in the placenta results in autolysis of the affected tissue, with the liberation of peptone, guanidine, and histamine as toxic split products of placental protein.

9. The amount and location of the infarction, the degree of vessel obstruction, and the rapidity of autolysis determine whether preeclampsia of mild or severe degree, eclampsia, or abruptio placentae will occur.

10. If hypercholesteremia is the fundamental basis for the toxemias of pregnancy, it would seem that prophylaxis should be directed toward neutralizing the effect of excessive secretion of cholesterol into the intestinal tract through the bile and preventing excessive storage of cholesterol in the endothelial system by the administration of thyroid extract or iodine and restricting the use of fats and cholesterol-containing foods during pregnancy.

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1040 Ponce de Leon Ave., N. E.

FETAL BLOOD STUDIES*

V. The Rôle of Anesthesia in the Production of Asphyxia Neonatorum

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THERE occur occasional cases of asphyxia neonatorum in which the obstetrician, for want of other explanation, incriminates the anesthesia given at the time of delivery. The studies of Leake,[1] of Ronzoni,[2] of Raginsky and Bourne,[3] and of others, indicate that in adults the common inhalation anesthetics produce decided changes in the acid-base balance of the blood and that nitrous oxide oxygen mixtures regularly cause varying degrees of anoxemia. It has been argued, indeed, that nitrous oxide owes its anesthetic effect largely to the associated anoxemia rather than to any intrinsic anesthetic quality.[4] The obstetrician has every reason to suspect that these blood chemical alterations extend to the child in utero, possibly with harmful effect, but actual studies of the question have been lacking. It has seemed to us that much of practical value might accrue if quantitative data were available, showing the effect of maternal anesthesia upon those constituents of the child's blood most directly concerned with the onset of respiration, particularly the oxygen content. To this end the present study was undertaken.

METHODS

With the mothers under various kinds of anesthesia, samples of umbilical cord blood were secured in the following manner. Immediately after the birth of the child, before the delivery of the placenta and prior to the onset of respiration, two Kelly clamps were placed on the cord close to the vulva and a second pair a few inches from the baby, all four clamps being applied as nearly simultaneously as possible. By cutting between the clamps at the two ends of the cord, a segment of cord about 12 inches long was usually obtained, tightly clamped at either end, and containing in its vessels enough blood for gas analysis. As soon as the piece of cord was obtained, blood samples from the umbilical artery and vein were drawn, the usual precautions being taken to protect the blood from contact with air and to prevent clotting. The oxygen analyses were carried out by the standard method of Van Slyke and Neill.[5]

The maternal blood specimens were taken from the arm vein and radial artery, as nearly as possible at the moment of delivery, the radial artery punctures being preceded by a local injection of novocaine.

In all, forty babies delivered under anesthesia were studied; in four cases the anesthetic was chloroform, in eight cases ether, and in twenty-eight cases nitrous oxide oxygen in various proportions. In addition, the bloods of fifteen infants delivered without anesthesia were analyzed as controls.

*Read, by invitation, before the Society of the Alumni of the Sloane Hospital for Women, November 1, 1935.

About half the anesthetics were administered by professional anesthetists and about half by members of the house staff. The four chloroform anesthesias were given solely for investigative purposes, but in all other cases the anesthetic was chosen which seemed best suited to the patient and was administered according to ordinary practice without reference to the contemplated blood study. Usually, indeed, the anesthetist did not know that the blood studies were to be carried out until a minute or two before the venipunctures were made. In the nitrous oxide oxygen anesthesias the relative quantities of the two gases administered during the last minute before the birth of the baby were estimated and recorded, but it is realized that these figures are approximations only. A particular effort was made to detect any maternal cyanosis occurring during the anesthesia.

Since it was desired to determine the effect of anesthesia per se upon the oxygen content of the child's blood, cases of breech extraction and difficult forceps delivery were excluded from the series in the belief that these procedures themselves might produce similar effects. Cases of birth injury or congenital defect were likewise discarded.

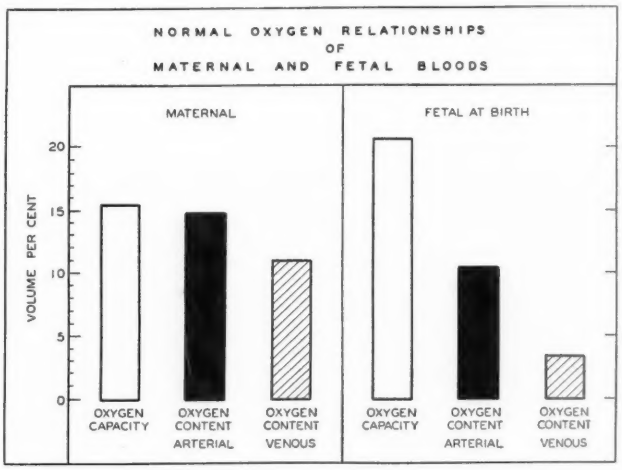

Chart 1.—Showing the average oxygen relationships of blood in fifteen normal mothers and fifteen unanesthetized infants at birth.

RESULTS

In evaluating the changes produced in fetal blood by maternal anesthesia, it is important to recall that the normal oxygen relationships of that blood differ widely from that of the adult. This is shown diagrammatically in Chart 1, which represents the average findings in fifteen mothers and in fifteen infants born without anesthesia. The contrast between the oxygen capacities of the two bloods is particularly striking, that of the full-term fetus averaging 20.8 volumes per cent and that of the mother 15.4 volumes per cent. Since the oxygen capacity of a given sample of blood is in direct proportion to its hemoglobin content, this finding simply confirms the well-known fact that blood of the newborn child is very rich in hemoglobin, whereas that of the average pregnant woman is slightly depleted of that substance. The arterial blood of the

fetus, conveyed to it through the umbilical vein, is low in oxygen as compared with that of the mother. At birth, in fact, its arterial blood contains on an average even less oxygen than the blood of the maternal arm vein. The low oxygen content of the umbilical vein blood becomes more striking if, instead of referring to the quantity of oxygen present in volumes per cent (c.c. of gas per 100 c.c. of blood), we express it as a percentage of the total amount of oxygen with which the blood will combine; or, in other words, in terms of percentage saturation. It will be seen then that while the arterial blood of the mother is usually 95 per cent saturated with oxygen and the maternal venous blood about 71 per cent saturated, the arterial blood going to the fetus at the moment of birth is only 50 per cent saturated with oxygen. A relatively large quantity of oxygen is given off by the arterial blood as it passes through the

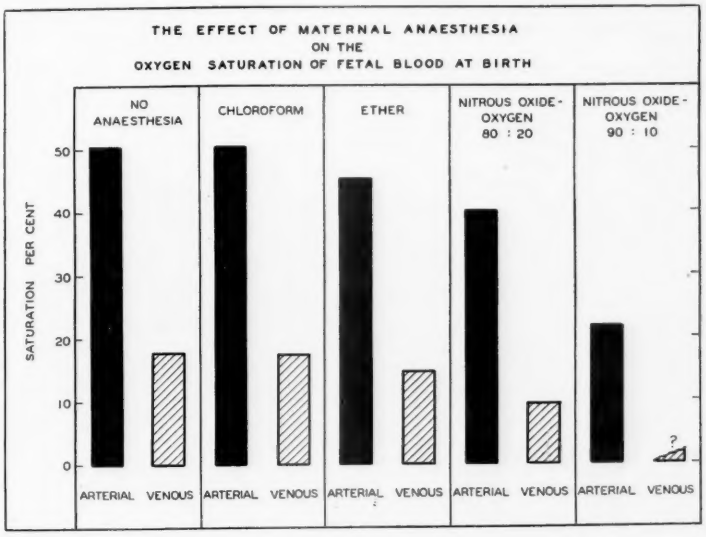

Chart 2.—Showing the average oxygen saturation of fetal blood at birth with the mothers under various kinds of anesthesia.

fetus, so that the venous blood returning from the fetus contains on an average only 3.3 volumes per cent of oxygen, a percentage saturation of less than 20 per cent. These figures represent the oxygen saturation of the arterial and venous bloods of infants born without anesthesia and are shown again, for comparative purposes, in the first two columns of Chart 2.

In the four cases of chloroform anesthesia, two of them low forceps deliveries and two spontaneous, no appreciable effect could be noted on the oxygen saturation of the fetal blood. This is in keeping with two well-known facts: first, since large quantities of air are given with chloroform, maternal anoxemia is not likely to result; second, since it is not highly irritating, the passage of air from the upper respiratory tract of

the mother to the pulmonary alveoli is not impeded by collections of mucus. And with the maternal blood well oxygenated one would not expect to find anoxemia of the fetus.

The average oxygen saturation of the fetal blood in eight cases of open ether anesthesia, all low forceps deliveries, was slightly depressed to 45 per cent in the arterial blood. The common tendency of ether to promote excessive secretion of mucus in the respiratory tract and consequent interference with the passage of air through the alveolar membranes of the mother is possibly responsible for this alteration, and in occasional cases very marked accumulations of mucus might conceivably produce greater changes. Usually, however, the diminution in the oxygen saturation of the fetal blood produced by ether is not of sufficient degree to injure the fetus through anoxemia.

CASE NO.	AGE	PARITY	GAS-MIXTURE APPROX	DURATION MINUTES	MATERNAL CYANOSIS	OXYGEN SATURATION OF BLOOD				ASPHYXIA
						MOTHER		CHILD		
						ARTERIAL	VENOUS	ARTERIAL	VENOUS	
1	29	III	80 : 20	2	NONE	% 92.1	% 70.5	% 41.0	% 20 3	NONE
2	19	I	85 : 15	3	NONE	90 7	68 7	38 4	-	NONE
3	18	I	85 : 15	5	SLIGHT	76 .2	50 3	25 1	16 0	NONE
4	25	II	80 : 20	2	NONE	90 6	-	51 9	26 8	NONE
5	25	V	80 : 20	2	NONE	-	-	40 5	19 9	SLIGHT
6	31	II	75 : 25	1	NONE	94 9	-	50 2	28 7	NONE
7	28	IV	75 : 25	2	NONE	-	-	51 3	30 0	NONE
8	20	I	80 : 20	4	PRESENT	68 .9	45 0	29 .2	18 1	SLIGHT
9	18	II	80 : 20	3	NONE	88 9	65 0	39 .2	-	NONE
10	28	III	75 : 25	2	NONE	93 .1	66 .6	44 4	19 8	NONE
11	19	II	80 : 20	2	NONE	-	-	44 0	-	NONE
							AVERAGE	41 .3		

Chart 3.—Showing the details of eleven cases in which nitrous oxide oxygen was administered for obstetric analgesia.

When we turn to the effects of nitrous oxide oxygen anesthesia upon the oxygen saturation of fetal blood, we meet more marked changes. In the eleven patients given nitrous oxide oxygen in the approximate proportions of 80:20, the actual gas mixtures received by the patient were probably somewhat higher than that shown, since the figure represents the concentrations given during the last minute of the second stage only and frequently stronger mixtures had been administered just previously. It was the desire in these cases to produce analgesia only. The twelve cases in which nitrous oxide oxygen in proportions of 90:10 was administered, comprised eight cesarean sections and four low forceps deliveries. In both these groups there was a substantial reduction in the oxygen saturation of the fetal blood, in the former the arterial saturation showing a moderate reduction to 40 per cent and in the latter group a decided decrease to 25 per cent, or one-half the normal figure. The venous blood

returning from the fetus in the umbilical arteries was likewise low in oxygen. It is thus clear that in the average case nitrous oxide oxygen anesthesia causes a considerable reduction in the oxygen content of the fetal blood, particularly when used in operative obstetrics. However, these average figures give us little insight into individual cases and fail to answer the important question, Does the anoxemia thus produced ever reach such levels as to endanger the child? This query can be met only by reviewing the figures which make up the averages set forth in the diagram.

In Chart 3 are shown the details of those cases in which the nitrous oxide oxygen mixtures approximated 80:20 proportions. In general, the bloods of these mothers showed only slight decreases in oxygen saturation, but in two instances, Cases 3 and 8, substantial reductions were

CASE NO.	AGE	PARITY	GAS-MIXTURE APPROX.	DURATION MINUTES	MATERNAL CYANOSIS	OXYGEN SATURATION OF BLOOD				ASPHYXIA
						MOTHER		CHILD		
						ARTERIAL	VENOUS	ARTERIAL	VENOUS	
1	19	I	85 : 15	12	NONE	% 76.7	% 49.4	% 25.2	% 10.1	NONE
2	27	II	90 : 10	20	SLIGHT	67.3	-	9.8	-	MODERATE
3	20	II	95 : 5	11	NONE	-	-	13.1	-	SLIGHT
4	22	I	85 : 15	18	NONE	80.9	-	31.7	-	SLIGHT
5	30	III	95 : 5	21	SLIGHT	69.1	-	10.3	-	MARKED
6	19	II	85 : 15	18	NONE	74.1	-	25.5	-	NONE
7	32	I	85 : 15	15	NONE	81.0	51.7	29.7	13.0	NONE
8	25	I	85 : 15	10	NONE	-	-	32.8	17.1	NONE
9	26	I	95 : 5	16	MARKED	49.2	-	11.7	-	SLIGHT
10	18	II	85 : 15	8	NONE	73.2	-	33.4	-	NONE
11	21	I	85 : 15	10	NONE	-	-	41.2	22.2	NONE
12	22	I	90 : 10	18	SLIGHT	66.8	40.4	17.1	-	NONE
CASES 1-8 CESAREAN SECTION. CASES 9-12 FORCEPS DELIVERY						AVERAGE		23.5		

Chart 4.—Showing the details of twelve cases in which nitrous oxide oxygen was administered for obstetric anesthesia.

observed and in both of these mothers a slight degree of cyanosis was noted. The arterial bloods of the infants in this group were characterized by rather wide variations in their oxygen saturation, the figures varying from 25.1 to 51.3 per cent. Previous observations, however, indicate that even oxygen saturations of 25 per cent are readily withstood by infants at birth, the typical case of severe asphyxia neonatorum showing a figure below 10 per cent. It would thus appear that nitrous oxide oxygen mixtures, given over short periods for analgesic purposes, do not produce a deleterious degree of fetal anoxemia. The same, however, cannot be said when stronger concentrations of the gas are administered for longer periods of time. As shown in Chart 4, when the proportions approximate or exceed 90:10 and are maintained for over ten minutes, both mother and child may manifest marked decreases in the

oxygen saturation of their bloods. Thus, in Cases 2, 3, 5, and 9, the arterial bloods of the infants revealed oxygen saturations of less than 14 per cent; in three of these cases, the gas mixture given the mother was in the approximate proportion of 95 : 5. In four of the twelve babies in the group there were varying degrees of asphyxia, but in only one instance was it marked. Evidence will be advanced presently, however, which suggests that the low oxygen saturations met in several of these infants, particularly Cases 2 and 5, represent dangerous levels of anoxemia. As might be expected, the bloods of the mothers in this group were substantially reduced in their oxygen content and in four instances varying degrees of cyanosis were present in the last minute or two before birth. It seems of particular importance to note that the umbilical arteries, carrying venous blood from the fetus, were collapsed in most of these infants, making it impossible to secure blood. We have ob-

CASE NO.	AGE	PARITY	GAS-MIXTURE APPROX.	DURATION MINUTES	MATERNAL CYANOSIS	OXYGEN SATURATION OF FETAL BLOOD AT BIRTH		ASPHYXIA
						ARTERIAL	VENOUS	
						%		
1	19	I	95 : 5	10	MARKED	1.5	VESSELS COLLAPSED	LOW FORCEPS HEART RATE 30 PER MINUTE DIED AFTER 15 MINUTES' ARTIFICIAL RESPIRATION
2	20	I	95 : 5	20	SLIGHT	6.0	VESSELS COLLAPSED	CESAREAN SECTION HEART RATE 28 PER MINUTE. DIED AFTER 25 MINUTES' ARTIFICIAL RESPIRATION
3	24	II	90 : 10	15	NONE	8.4	VESSELS COLLAPSED	LOW FORCEPS APNEA 20 MINUTES
4	17	I	95 : 5	20	SLIGHT	7.3	VESSELS COLLAPSED	LOW FORCEPS APNEA 15 MINUTES
5	30	III	95 : 5	18	SLIGHT	10.4	VESSELS COLLAPSED	LOW FORCEPS APNEA 15 MINUTES

Chart 5.—Showing the details of five cases of profound asphyxia neonatorum in which concentrated mixtures of nitrous oxide oxygen had been administered to the mothers.

served this collapsed state of the umbilical arteries again and again in cases of marked fetal anoxemia and regard it as rather a constant characteristic. Presumably it is due to a fall in the arterial blood pressure of the infant in connection with the anoxemia.

But the question remains to be answered whether nitrous oxide oxygen anesthesia ever produces really profound, or actually fatal asphyxia neonatorum. It was hardly to be expected in prearranged studies such as this that we would encounter a case showing such a relationship. Accordingly, this scheme of attack was planned. The clamped umbilical cords of all babies born by operation under nitrous oxide oxygen anesthesia were momentarily saved, previous experiments indicating that the fetal blood showed no appreciable changes under such circumstances. If the baby breathed at once or after a few minutes, the cords were dis-

carded, but if severe asphyxia ensued the umbilical blood was analyzed for oxygen. Naturally, such samples of blood sometimes came from cases of cerebral hemorrhage or congenital defect, but over a period of years five cases have been collected in which there was no demonstrable organic cause for the baby's inability to breathe. Some details of these five cases are shown in Chart 5. In the first two cases, the babies died after prolonged artificial respiration and autopsy revealed no explanation for the deaths. The anesthesia mixtures used in these two instances were 95 per cent nitrous oxide and 5 per cent oxygen; in Case 1 the administration of the anesthetic was said to have been very "troublesome" with marked maternal cyanosis resulting. The exceedingly low figure for the oxygen saturation of the arterial blood of the infant in Case 1 was doubly checked and indicates that all oxygen combined with hemoglobin had disappeared, leaving only a negligible quantity in solution in the serum. In Case 2 the arterial blood of the infant was likewise almost depleted of oxygen. Although the babies in the remaining three cases survived, they showed the picture of profound asphyxia neonatorum and required prolonged resuscitation. The highest arterial oxygen saturation in these five infants was 10.4 per cent and the average was 6.7 per cent. The latter figure is equivalent to about one volume per cent of oxygen or approximately one-tenth of the amount found normally at birth and one-twentieth that present in the arterial blood of the adult. As usual in severe asphyxia neonatorum, the umbilical arteries were completely collapsed.

COMMENT

The results of this study would seem to justify the conclusion that nitrous oxide oxygen anesthesia, administered to the mother in concentrations sufficient for operative obstetrics, *occasionally* reduces the oxygen content of the umbilical blood to extremely low levels. Lack of oxygen kills tissues as quickly as many active poisons, and it is only reasonable to assume that such levels of anoxemia as we have described exert harmful and even fatal effects on the child at birth. This assumption, indeed, is implied in our very term asphyxia neonatorum. But it is seldom recalled in viewing a grave case of asphyxia at birth, with the slow heart rate, the cold, white body, and the limp extremities, how precisely, how completely the clinical picture duplicates the reaction of any organism to anoxemia. In experimental animals, as well as in man, anoxemia has been the object of intensive study for over half a century. But, whether we consider the studies of Klug of Germany in 1883,[6] of Lewis and Mathison of London in 1910,[7] or of Greene and Gilbert of the United States in recent years,[8] the results are the same; on few subjects has there been such complete agreement, for experimental anoxemia produces a constant, clear-cut train of phenomena which may be reduplicated in the laboratory at will. The sequence of events may be described

as follows: To mild degrees of anoxemia the body reacts by increased respiration and accelerated heart rate; these presumably are compensatory mechanisms, the first designed to bring more oxygen to the blood and the second to deliver more oxygen to the tissues. With increasing anoxemia a point is reached when these compensatory mechanisms fail to supply oxygen in amounts sufficient for cellular oxidation and then with dramatic suddenness, "the oxygen crisis" of the physiologists, or what is termed "the reversal" by Schmidt,[9] takes place and after this, events occur rapidly. Consciousness is lost and respirations stop. Following respiratory failure there is an interval of from three to five minutes during which the heart continues to beat; but there is a marked slowing of the rate. In a typical case the slowing occurs by abrupt steps from 156 per minute before the crisis to 44 per minute in the post-crisis phase. Electrocardiographic studies of the heart at this stage show suppression of the pace-making function of the sinoauricular node and the assumption of that function by the auriculoventricular node with its characteristic slow and regular rate. There is regularly partial or complete heart block with decrease in conduction in the internodal region to the point of suppression. Since this slowing of the heart in anoxemia does not occur in animals with the vagi cut, it is apparently due to vagospasm, which suppresses the sinoauricular rhythm. After respirations cease, sometimes a little earlier, the blood pressure slowly declines through forty to sixty seconds. It then may show a slight increase, but finally falls rapidly through two to three minutes, then more slowly for one or two minutes until a systolic pressure of 15 to 20 mm. Hg is reached. Concomitant with the drop in blood pressure the skin becomes blanched and cold, as in shock. Early in the post-crisis phase of experimental anoxemia another important change occurs: the nerve muscle endings of skeletal muscle cease to function, with complete collapse of that muscular system. Finally, it may be noted that a few whiffs of oxygen or air, administered by artificial respiration, restores the animal at once to normal provided this is done within three or four minutes following the oxygen crisis. To summarize the picture of experimental anoxemia in the post-crisis phase, there occur in rapid succession loss of consciousness, cessation of respiration, marked slowing of the heart, fall in blood pressure with the white, cold skin of shock and skeletal muscle collapse. Surely, few clinical conditions can be simulated so completely as can asphyxia neonatorum by experimental anoxemia.

Since the time of Ahfeld[10] it has been generally believed that the thoracic wall and diaphragm of the fetus make shallow, rhythmic excursions throughout the latter part of intrauterine life. Two of my associates, Dr. F. F. Snyder of the Department of Obstetrics and Dr. Morris Rosenfeld of the Department of Pharmacology and Experimental Therapeutics, are now engaged in an experimental study of this phenomenon in rabbits. By means of an ingenious technic, they are able to

watch these fetal respiratory movements closely, and they find that their rate increased during the latter part of pregnancy from a very slow one to about 60 per minute at term. Although their studies are not yet complete, they have permitted me to say that the effect of maternal anoxemia on these movements is clear-cut. As the oxygen supply to the mother is diminished, the rate of the movements becomes slower and with extreme anoxemia they stop. If now, the fetuses are delivered at term under these circumstances, the onset of respiration either fails or is much delayed.

In interpreting the results of our study in terms of practical anesthesia in the delivery room, considerable caution is necessary. Certainly, the skill and judgment of the anesthetist and the behavior of the individual patient enter so largely into the problem that hard and fast rules are impossible. A few generalizations, however, would seem permissible. In the first place, it should be emphasized that chloroform, despite its benign effect on the child, has proved too dangerous to the mother to have an important place in operative obstetrics. Since ether passes readily through the placenta, it must exert considerable anesthetic effect upon the child, and we believe it is due to this influence and not to anoxemia that the occasional "etherized" baby is slow in starting to breathe. Provided there is no cerebral injury, however, we find that these infants react well to time and gentle stimulation. Certainly in our opinion, their prognosis is immeasurably better than those in which the apnea is the result of profound anoxemia. Our figures show clearly that nitrous oxide oxygen anesthesia for periods of less than five minutes and in proportions of 85:15 or weaker, does not cause a harmful degree of anoxemia. The time element here is most important and pure nitrous oxide, administered for four or five breaths to produce analgesia, probably causes less anoxemia than a mixture of 85:15 continued for five minutes. But it is on the problem of anesthesia in operative obstetrics that our study would seem chiefly to bear. Here it seems plain that when nitrous oxide oxygen is given in concentrations of 90:10 or stronger over periods which exceed five minutes, marked degrees of anoxemia are produced in about one baby out of every three. The anoxemia may not prove harmful, it is true, but in the exceptional case, as we have shown, it may be associated with profound and even fatal asphyxia neonatorum. It is not intended by this statement to exclude nitrous oxide oxygen from the field of operative obstetrics. The criticism is only of the very concentrated mixtures given without ether for periods which exceed five minutes. An adequate saturation of the fetal blood with oxygen can be guaranteed only if the mother receives fifteen parts of oxygen in every 100 parts of the gas mixture, and to satisfy this end, ether should be added to the gas mixture if the latter, in proportions of 85:15, does not suffice. After prolonged labors, in particular, babies seem to withstand anoxemia poorly, and if an operation is necessary in

such cases, we prefer ether on an open mask to insure liberal oxygenation of the child's blood. The same is true of breech extractions in which there is an inherent tendency to fetal anoxemia due to the impingement of the child's shoulders and head on the umbilical cord.

In sum, we hold to the belief that asphyxia neonatorum, in all of its manifestations, is an example of profound oxygen want. For this reason the one urgent necessity in its treatment is oxygen, and by the same token, the one urgent requirement in its prevention is oxygen.

CONCLUSIONS

1. Chloroform anesthesia, when administered to mothers at the time of delivery, has no demonstrable effect on the oxygen saturation of fetal blood, but due to its toxic effects on the mother, it is not to be recommended as an obstetric anesthetic.

2. Ether anesthesia produces a slight depression of the oxygen saturation of fetal blood, but this is not of sufficient degree to injure the fetus through anoxemia.

3. Nitrous oxide oxygen mixtures, administered to mothers in proportions of 85 : 15 or weaker, and for periods of less than five minutes, regularly cause moderate degrees of fetal anoxemia but the normal, full-term infant is apparently not harmed.

4. When nitrous oxide oxygen is given in concentrations of 90:10 or stronger over periods which exceed five minutes, marked degrees of fetal anoxemia are produced in about one baby out of three and occasionally profound asphyxia neonatorum results.

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THE PERIOD OF PUBERTY AND THE INCEPTION OF MENSTRUATION*

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THE age of puberty represents a very critical time in the life history of every young woman. It is a period which eventuates into maturity, and it is accompanied by a number of important changes in the organs of internal secretion, by the development of the secondary sexual characters, by the cessation of increase in stature and by a psychic transformation. The beginning of menstruation, the menarche, is also a striking event at this time, and a number of menstrual disorders are particularly prone to occur during the first few years. In order to understand the full significance of these disturbances it is necessary to consider a number of important facts which deal with the relation of the menarche to other events of the pubertal age, as well as to appreciate the wide variations in the character of the early menstrual periods which may occur under normal conditions.

AGE AT ONSET OF MENSES

Since the days when Brierre de Boismont first made a statistical study of the age of onset of puberty and computed an average figure, this problem seems to have possessed a peculiar fascination for a large army of clinical investigators. The literature abounds with scores of studies, many based upon thousands of subjects, but most unfortunately valueless for purposes of comparison and also open to doubt as to their scientific accuracy. This is due in great part to the prevalent method of obtaining the ages of the subjects, which depends usually on the doubtful recollections of adult women questioned by junior assistants in large gynecologic clinics. Although a number of studies based on the careful observation of schoolgirls are now available, the series are not large, and, as Kennedy[1] points out, the sampling error in such groups is too great to allow the figures to represent any final conclusion. The different ways of expressing age classes by various authors also render many of the reports useless for comparison with one another.

*Address delivered before the Harbor Branch of the Los Angeles County Medical Society, Long Beach, California, October 25, 1935, and the San Francisco Bay Counties Obstetrical and Gynecological Society, February 14, 1936.

On the basis of information at present available, it would seem that in the vast majority of American girls the age at first menstruation varies from ten to seventeen years, and the average has generally been found to be somewhere between thirteen and fourteen (Engelmann,[2] Baldwin,[3] Lintz and Markow,[4] Hotelling,[5] Popenoe,[6] Gould and Gould,[7] Boas,[8] Engle and Shelesnyak,[9] and others). On the other hand, reports from various European countries indicate that the average age of the menarche is from fifteen to seventeen, one to two years later than in the United States.

Many students of this problem have sought to compare various series in order to determine the conditions that influence the age at which puberty appears. The multiplicity of factors concerned in such analyses provide objections which seriously impair the validity of many far-flung conclusions which have been advanced. It has, for instance, been widely maintained that *climate* has an important influence on the age of puberty, but a consideration of reports from many localities fails to produce convincing evidence. The subject deserves more careful investigation, however, and Mills[10] has recently pointed out that since the European immigrant stock in the United States gradually approaches the earlier North American Indian age some factor of environment must be responsible for the change, and he believes that the element of weather variability may be important. This is also supported by the observation of Engle and Shelesnyak,[9] who demonstrated a distinct seasonal incidence in the onset of the first menses, as only 18 per cent of the total number of subjects (American) they studied occurred during the summer months of June, July, and August.

The question of *race* has been considered by several authors, and it has been asserted that in certain localities an earlier menarche is found among Jewesses than among the Gentiles (Schaeffer,[11] Weissenberg,[12] Bolk[13]). The original work of Schaeffer[11] also suggested that *social status* may have an important bearing on the problem. He found that among the upper social strata the average age of the menarche was almost two years less than among women of the lower classes, and the probable importance of diet (Slonaker and Card[14]) and hygiene leads to a serious consideration of this observation. Similarly, he claimed that the figure for women living in large cities generally was less than for those from rural districts, but the studies of Engelmann[2] and Lintz and Markow[4] do not point to such influences as active in this country.

An observation which seems to have been authenticated both in Europe and the United States (Bolk,[13] Popenoe,[6] Gould and Gould[7]) is that the daughters of the present generation have an earlier menarche than their mothers. This is particularly of interest in view of the relation of the onset of menstruation to general body growth, and the finding of Boas[15] that the stature of the children of the year 1921

was increased over that of the children of 1888. These studies also demonstrate that a tendency of the mothers to menstruate early or late is repeated to some extent in the offspring, and are thus in keeping with the contention that the age of attainment of puberty is an *hereditary* character (Crew[16]).

The effect of *constitution* on the early or late appearance of the menses has also been considered. Bolk[13] found that blondes, as determined by the color of skin and hair, had an average age of onset of puberty of almost one year less than did brunettes. A similar finding was recorded by Schaeffer,[11] although he noted a much less significant difference between the two groups.

Since it might be conjectured that childhood marriage with its consequent early stimulation of the genital organs could lead to an earlier appearance of the menses, it is impressive that no such relation could be established by Curjel[17] among Indian women.

The age of onset of puberty is thus a very variable characteristic. An analysis of the factors which may influence it, climate, race, environment, social status, heredity, as well as personal elements such as diet and hygiene, renders the problem exceedingly complicated. However, it is desirable that further light be sought since the early or late appearance of menstruation undoubtedly represents a constitutional trait of considerable significance.

THE MENARCHE, BODY GROWTH, AND SECONDARY SEXUAL CHARACTERS

The life of an individual may be divided into three chief phases: first, a period of growth which includes intrauterine development and the changes occurring in the body from birth to adulthood; second, a period of maturity; and third, a period of retrogression, or senescence. The transition either from the first to the second, or from the second to the third of these stages is associated with a series of changes which occupy a number of years and vitally affect the individual concerned. In women, the inception of menstruation at the age of puberty, or the cessation of the menses at the climacteric, not only provide important landmarks which are readily observed, but each has always been accepted as the actual climax of the first and second periods of life, respectively. The work of recent years, however, has cast doubt on the correctness of this interpretation (Biedl,[18] Steinach and Kammerer,[19] Crew,[16] Hartman[20]), and in any consideration of puberty it is important to recognize the relation of the appearance of the first menses to certain other manifestations of this transition period.

It has long been known that a close connection exists between somatic and sexual development, and it is well illustrated by the sudden increase in the rate of body growth, the "Zweite Streckung" of Stratz, which occurs as adolescence approaches. This period, the "age of

maximum rate of growth," not only bears a very definite relation to the first menses, but varies in intensity and time of occurrence according to the age of the menarche (Boas[8]). In a group of schoolgirls, Boas[8] found that the average age at first menstruation was 13.1 ± 1.2 years, while the moment of the most rapid rate of growth was 12.0 ± 1.2 years. There is thus an average difference of about one year between the two ages, although this actually varies according to the early or late onset of puberty. "Maximum growth occurs between ten and eleven years for those with first menstruation between ten and twelve; between eleven and twelve for those with first menstruation between twelve and thirteen years; and between twelve and thirteen years for those with first menstruation between thirteen and seventeen" (Boas[8]).

Since the period of maximum growth precedes the first menstruation, girls at the menarche are generally taller than the average in

Fig. 1.

dividual of the same age. However, since the growth period is the more intense the earlier puberty sets in, this difference is much more marked in younger adolescents.

By way of illustration we have the study of 151 schoolgirls reported by Baldwin[3] (Fig. 1). He found that 7 girls who first menstruated at eleven years of age had an average height of 148.2 cm., while the average or normal for the school at that age was 140.39 cm.; 25 girls with first menstruation at twelve years of age had an average height of 152.1 cm., with the average or normal for the school at 146.22 cm.; 56 girls with first menstruation at thirteen years of age had an average height of 155.3 cm. and the normal was 152.74 cm.; 42 girls with first menstruation at fourteen years of age had an average height of 159.6 cm. and the normal was 156.97 cm.; 17 girls with first menstruation at fifteen years of age were 158.5 cm. in height and the normal was 159.35 cm.; and 4 girls with first menstruation at sixteen or a comparatively late age were 163.2 cm., while the average for the group was 161.59 cm.

Following the period of maximum rate of body growth and the initiation of the menses, there is a rapid decrease in growth until it

practically ceases within one to three years (Table I). In keeping with the previous observations, the earlier the onset of puberty the more rapid is the completion of growth processes, and hence individuals who begin to menstruate while very young tend toward a short stature as adults.

TABLE I. PERCENTAGE OF SCHOOLGIRLS WHO CEASE GROWING AT A GIVEN AGE. (BOAS)

AGE AT FIRST MENSTRUATION	NO. OF CASES	AGE AT WHICH GROWTH CEASES			
		14	15	16	17 and later
10-11	13	50	50	--	--
11-12	49	--	27	56	17
12-13	103	6	40	27	27
13-14	181	10	3	38	49
14-15	104	--	5	40	55
15-16	45	--	--	15	85

The relation of the appearance of the extragenital secondary sexual characters to the onset of menstruation has been studied in large groups by Ploss and Bartels,[21] Stratz,[22] Weissenberg,[12] Godin,[23] Demmé,[24] Rosenstern,[25] and others, and more recently Priesel and Wagner[26] have reported their findings in individual cases followed over a number of years.

Although the development of these characteristics overlaps and they progress simultaneously until maturity has been reached, a definite order is discernible in their first appearance. Until the age of seven or eight the growth of male and female children remains essentially similar, but subsequently sexual differentiation begins. This manifests itself as early as eight to ten years of age in the development of the female pelvis, which now assumes wider proportions and is accompanied by a deposition of fat over the hips, and later, over the shoulders, thorax, and pubis.

The differentiation of the female breasts, consisting of an elaboration of the duct system, deposition of fatty tissue and development of the areola and nipples, may begin as early as the tenth or the eleventh year. In a group of children studied by Demmé,[24] evidence of beginning breast development was found in 2 per cent of children at ten years of age, in 18 per cent at eleven, in 43 per cent at twelve, and in 75 per cent at thirteen years of age. Priesel and Wagner[26] assert that full development is attained in from three to four years and is invariably far advanced at the time of the first menses. However, Dieckmann[27] has also observed that histologic differentiation is not complete until about the twentieth year.

The growth of hair over the symphysis pubis generally sets in after the breast changes have made their appearance, and it is also present

at the time of first menstruation. However, hair may not develop in the axillae until later, after the menarche, although Priesel and Wagner[26] note exceptions when it appears very early.

FUNCTIONAL SIGNIFICANCE OF THE MENARCHE

The inception of menstruation can thus in no way be considered as the end point of the pubescent age nor as the factor which initiates the changes of this period. In addition, there is evidence which suggests that the menarche does not even represent complete sexual maturity.

Mirskaia and Crew[28] found that in the mouse the onset of the first estrus was followed by a period of adolescence during which only a small percentage of females conceived, there were many incomplete pregnancies, and the mothers exhibited a tendency to eat their young. A related phenomenon was observed in the rhesus monkey by Hartman.[20] Fifteen females averaged 3,350 gm. in body weight at the time of the first menses, and although most of them were mated soon after puberty, not a single one conceived until an interval of about one year had elapsed and they had attained a weight of 4,370 gm.

Hartman[20] has recently pointed out that a relative sterility probably exists in women during adolescence in spite of the existence of occasional instances of gestation in very young individuals. Vignes[29] states that "the inception of menstruation does not necessarily mean the capacity for conception; many girls who are just beginning to menstruate would conceive with difficulty." Hartman[20] has also drawn attention to a number of observations made in countries where marriages take place at the time of puberty, and they indicate that conception does not occur for an average of about three years after the onset of the first menses. He quotes a gynecologist, Mondière, who "spent some years in Cochin China, where he gathered certain data (first menses, first parturition, number of children, menopause, etc.) concerning 960 Annamite, 106 Chinese, and 87 Cambodian women. He found that the first menstruation took place on the average at 16¼ years in the Annamites, at 16½ in the Chinese, at 16 10/12 in the Cambodians; the first parturition in these groups at 20½, 16 10/12, and 22½ years respectively, despite their early marriages." Malinowski[30] likewise noted that among the Trobiand Islanders pregnancy among young unmarried girls is extremely rare despite the absolutely unrestrained and promiscuous sex life which begins in childhood.

The fact that the inception of cyclic uterine bleeding in the human adolescent is not necessarily coincident with the acquisition of the ability to successfully bear children is of considerable biologic importance. The problem is in some ways related to the induction of "precocious sexual maturity" in laboratory animals by the administration of anterior pituitary substances, and it seems evident, as Engle[31] states, that a general somatic maturity is essential for the establishment of a complete reproductive potential.

ENDOCRINE GLANDS

Since all the manifestations of the pubescent and adolescent periods are considered as due to the activity of the glands of internal secretion, it is inevitable that attention should be directed to these organs

at this time. There are distinct morphologic changes in the ovaries, a significant increase in the weights of the thyroid and adrenal glands, and the involution of the thymus begins. On the other hand, the anterior lobe of the hypophysis, which apparently plays a most important rôle, shows no definite modification of its size or histologic appearance.

On the basis of numerous experimental studies and clinical observations, there is no doubt that the changes associated with puberty are directly attributable to the action of the anterior hypophysis, the thyroid, and the gonads, while the thymus exerts an influence which is not yet fully understood. The operation of hypophysectomy in young experimental animals is followed by a cessation of body growth and an atrophy of the genital organs, and the administration of anterior pituitary extracts or of fresh gland tissue results in excessive skeletal growth and increased development of the sex glands. The removal of the thyroid in immature animals may markedly interfere with body growth and the development of the gonads, but since the same phenomenon also occurs when a hyperthyroid condition is produced, its rôle may simply consist of acting as a controlling influence. The ovaries are directly concerned with the development of the accessory genital organs and the secondary sexual characters. And finally, the recent experiments of Rowntree et al.,[32] who induced precocious maturation by the injection of thymus gland extract in successive generations of rats, demonstrate that this organ has some important function associated with puberty.

On the other hand, the exact rôle of the endocrines and the complexity of their interaction which leads to somatic and sexual maturity are still far from solution. Until such information is available there is a serious handicap to the proper understanding of the disorders of this period, but it must be remembered that we are dealing with processes which affect the whole body, and attention cannot be directed solely to the pelvic organs.

CHARACTER OF EARLY MENSTRUAL PERIODS

Although it has long been held that the normal menstrual cycle is twenty-eight days in length and any variation from this standard must be considered as pathologic, recent years have seen a radical departure from this standpoint. It is now clearly recognized that in the majority of women there is a great variability in the lengths of successive cycles, and that this is consonant with normalcy (Fluhmann[33]). For this reason it is not surprising to find this irregularity more marked during the years of puberty (Paton,[34] Knaus,[35] Engle and Shelesnyak,[9] and others), and that it generally manifests itself by a lengthening of the cycles so that in many instances months may intervene between successive periods.

In a study of 3,140 menstrual cycles in 100 pubescent girls, Engle and Shelesnyak[9] found a great variability. The cycles ranged from 7 to 256 days with the mode at 28 and a mean of 33.9, and while the variability of the earliest menstrual cycles was higher it decreased with menstrual age. There were many periods of amenorrhea, since 202 out of the 3,140 cycles were more than fifty-seven days in length, and these were more prone to occur during the summer months.

TREATMENT OF MENSTRUAL DISORDERS

In spite of the many important facts brought to light by investigations of the past few years, there is still much obscurity regarding the significance of many of the changes of the pubescent period. It seems definitely established, however, that the appearance of the first menstruation is merely one of a series of events which culminate in a few years in complete somatic and sexual maturity. In the interval, the menstrual cycles are characterized by great irregularity in length, are frequently interposed by long periods of amenorrhea, and, in view of the comparative sterility, are incomplete from a functional standpoint.

It is very important to keep these facts in mind in considering the menstrual disorders of this period. A careful examination must always be conducted in order to eliminate any systemic condition or organic pelvic disease, but in most instances no specific therapy is indicated. This applies particularly to cases of amenorrhea or delayed appearance of the menarche, but it should be remembered as a general principle which applies to all "functional" menstrual disturbances of the puberty. If, however, it should be deemed advisable to treat such patients, general hygienic measures, diet, exercise, should be employed. By such methods, for example, Clow[36] was able to decrease the incidence of severe dysmenorrhea in schoolgirls from over 40 per cent to less than 6 per cent. The use of gonadotropic hormones or estrogenic substances is not warranted except in certain types of uterine bleeding. The administration of thyroid extract, however, remains one of the most valuable therapeutic agents, and careful investigation should always be made for the existence of a hypothyroid state.

Menorrhagia and metrorrhagia are especially prone to occur during the years of puberty, and are invariably due to hyperplasia of the endometrium (Wolfe[37]), which results from an ovarian deficiency characterized by a growth of follicles and an absence of ovulation and corpus luteum formation. This condition is of special interest in view of its resemblance to the "anovulatory cycles" of monkeys (Fluhmann[38]), which occur with greater frequency during puberty, and which Hartman[20] considers as the explanation for the comparative sterility of this period. Although it is not possible to determine with certainty the incidence of hyperplasia endometrii in young women, there are some suggestive clinical signs which may be employed in

approaching this problem. For instance, a young woman of nineteen under treatment for prolonged uterine bleeding gave a very definite history of two "types" of menstrual periods. The more frequent type, suggesting a normal cycle, was characterized by a flow lasting four to five days, moderate in amount, and accompanied by severe cramps. The second variety, which may represent cyclic bleeding due to hyperplasia endometrii, occurred at varying intervals, either alternating with the first or following several such cycles, lasted considerably longer, was much more profuse in amount, and was *not* associated with cramplike pain.

The treatment of uterine hemorrhages at the time of puberty, in the absence of organic lesions, should consist of general measures as mentioned previously, but in addition certain procedures must be followed to control the bleeding. It may be necessary to perform a curettage and even repeat it at intervals, but in most instances the bleeding can be controlled by the daily injection of large loses of chorionic gonadotropic hormone ("anterior pituitary-like" factor). The administration of thyroid extract may prove of value (Lisser[39]). In our experience it is very seldom necessary to resort to radical procedures such as hysterectomy or irradiation.

SUMMARY

The period of *puberty* represents a transition from the period of growth to complete somatic and sexual maturity. The *menarche*, or the appearance of the first menstruation, is a single event in the course of puberty. It does not denote either the end point or the beginning of the pubescent period. It bears a definite relationship to body growth, but the development of the secondary sexual characters begins before and continues after the first menses. The menstrual cycles during the first few years are characterized by marked irregularities, are frequently separated by long periods of amenorrhea, and are functionally incomplete, since a comparative sterility probably exists. With the exception of abnormal uterine hemorrhage, the treatment of functional menstrual disorders during this time should consist primarily of general hygienic measures rather than of attempts to directly influence the pelvic organs.

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STATISTICAL STUDIES ON PUERPERAL INFECTION

II. AN ANALYSIS OF 545 CASES OF PUERPERAL INFECTION (INCLUDING A COMPARISON BETWEEN THEM AND A SIMILAR GROUP OF CASES WITH NORMAL PUERPERIA)

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IN A previous communication the author presented an analysis of the occurrence of puerperal infection in 5,767 consecutive term deliveries. This first paper dealt with the factors influencing the incidence of puerperal infection. In order to amplify this study and to further emphasize certain of its conclusions, it seemed of value to examine carefully the history, clinical course, and laboratory examinations in a series of patients developing a frank intrauterine infection during the puerperium. Furthermore, in order to provide a suitable comparison, an analysis was also made of a similar group of women whose puerperia showed no febrile reaction. The results of these analyses and their correlations comprise this second statistical study of puerperal infection.

These cases of puerperal infection to be analyzed consist of 545 patients delivered at or near term on the Obstetrical Service of the Johns Hopkins Hospital from Sept. 12, 1925, to Aug. 24, 1933, excluding all cases of cesarean section. The course after delivery in all of these patients satisfied the criteria employed in this Clinic for the diagnosis of puerperal infection: namely, a temperature of 100.4° or above on two or more days, not necessarily successive and excluding the first twenty-four

hours after delivery. Moreover, such conditions as pyelitis, mastitis, respiratory infection, etc., were clinically excluded as the sole cause of the fever, although in certain instances they were present as a complicating factor; and in each case positive clinical or bacteriologic evidence of the intrauterine infection was adduced. As a contrast to this series we selected at random 500 case histories of patients delivered during the same time period but whose puerperia were normal in every way. Again, instances of cesarean section were excluded from the group. These two groups of cases were taken from the general clinic material, which is divided about equally between the white and black races and which contains less than 10 per cent private patients. It is felt that so far as predisposing factors such as race, social status, etc., are concerned, the two series of cases are strictly comparable.

It is our purpose first to compare the two groups of cases in respect to certain facts of the clinical history and course of labor, making necessary subdivisions for each separate analysis. Finally, we will present a special analysis of the abnormal group in terms of certain signs and symptoms coincident to the infection.

COMPARISON BETWEEN THE GROUPS OF INFECTED AND NONINFECTED CASES

1. *Make-up of the Series According to the Duration of Pregnancy and Type of Delivery.*—Table I presents the make-up of the two series of cases according to the duration of pregnancy and type of delivery. It will be noted that less than 5 per cent of the deliveries in either group

TABLE I

TYPE OF DELIVERY	PER CENT OF TOTAL CASES	
	P. I.*	NORMAL
F. T. S.*	65.69	77.67
F. T. O.	29.54	17.75
Pr. S.	3.30	3.05
Pr. O.	1.47	1.53

*In this and the succeeding tables the following abbreviations will be used: F. T. S., Full-term spontaneous; F. T. O.; full-term operative; Pr. S., premature spontaneous; Pr. O., premature operative; P.I., puerperal infection.

were premature according to the classification employed at this Clinic, which postulates that a premature child is at least 1,500 gm. in weight or 35 cm. in length and not over 2,500 gm. in weight or 45 cm. in length. The difference between the two series is entirely due to a much higher operative incidence among those patients developing puerperal infection.

2. *Color of Patient.*—The increased incidence of puerperal infection among black women as contrasted with white has already frequently been pointed out, the figures shown in Table II serving to emphasize this point. It should be noted that with spontaneous delivery at term, although slightly less than half of the patients in the normal group were colored, yet seven-tenths of those developing signs of infection were of that race.

It has been our general experience that the incidence of operative delivery is higher in the white than in the black race despite the fact that pelvic contraction occurs three times as often in the latter group of patients, and accordingly it will be noted in Table II that with operative delivery white patients predominate in both the normal and the

TABLE II. PER CENT OF TOTAL CASES

COLOR	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
White	29.53	51.45	54.43	68.54	38.40	53.60
Black	70.47	48.55	45.57	31.46	61.60	46.40

puerperal infection groups. However, in the latter group the incidence for the two races was almost equal, while in the former (normal puerperium) more than two-thirds of the patients were white; an observation which again demonstrates the decreased resistance of the black woman to puerperal infection.

3. *Age of Patient.*—Table III further illustrates the fact that with advancing age there seems to occur an increasing resistance to puerperal infection, and it might be added that, although not shown in the table, a similar discrepancy exists between the normal and infected groups

TABLE III

	MEAN AGE IN YEARS		PER CENT YOUNG PRIMIPARAS		PER CENT ELDERLY PRIMIPARAS	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
F. T. S.	21.76	23.47	13.45	7.62	0.58	0.25
F. T. O.	23.37	25.46	10.13	7.53	1.90	3.23
Pr. S.	22.78	24.38	0.00	0.00	0.00	0.00
Pr. O.	25.00	26.25	12.50	12.50	0.00	0.00
Total	22.32	23.89	11.98	7.44	0.95	0.76

when primiparas alone are considered. Moreover, the incidence of young primiparas (aged sixteen years or less) is much higher in the febrile group although the difference between the two series when elderly primiparas (aged thirty-five years or more) are considered is so small as to be within the limits of sampling error.

4. *Parity of Patient.*—The material of a teaching clinic usually contains an abnormally high percentage of primiparas as contrasted with

TABLE IV. PER CENT OF TOTAL CASES

PARA	F. T. S.		F. T. O.		TOTAL INCLUDING PREMATURES	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
i	71.51	54.29	79.50	64.53	72.66	55.36
ii	10.89	18.67	6.83	11.83	10.09	17.73
iii	6.98	9.09	2.48	5.37	6.24	8.41
iv, v	4.19	8.35	1.86	4.30	3.67	7.81
vi, vii	3.35	4.44	1.86	8.60	3.12	5.34
viii, ix	1.96	2.22	3.73	5.37	2.39	2.86
x and over	1.12	2.94	3.73	0.00	1.83	2.49

the childbearing population as a whole, and in accordance with this, 55 per cent of the total normal group were pregnant for the first time. In the series of women with puerperal infection the incidence of primiparas was considerably higher and totalled 72.66 per cent, a discrepancy which is partially explained by the increased number of operative deliveries in this class of patients. However, it seems clear that this factor is not the only one since, when only those patients delivered spontaneously are considered, the percentage of primiparas is still much higher in the infected than in the normal group, and is 71.51 and 54.29, respectively.

5. *Time of Admission to Hospital.*—It seemed reasonable to assume that the further labor progressed before the patient was admitted to the hospital the greater might become the chance of an ensuing puerperal infection, and it was in an effort to investigate this premise that the analysis shown in Table V was made. The duration of labor at the time of admission was arbitrarily catalogued as early or late, with one-half of complete cervical dilatation being chosen as the dividing point. A

TABLE V. PER CENT OF TOTAL CASES

	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
Before onset of labor	19.35	14.82	31.33	27.95	23.60	17.62
Early, cervix 0-4 cm.	62.17	58.27	49.33	62.38	57.06	58.06
Late, cervix 5-9 cm.	18.47	26.91	19.33	9.67	19.34	24.32

study of Table V would not seem to confirm the assumption made at the beginning of this paragraph, although certain modifying factors are to be found. In the first place, those patients admitted prior to the onset of labor comprise an abnormal group, since their admission was usually necessitated by premature rupture of the membranes, postmaturity, or some obstetric complication. It is our intention to deal with the effects of the time of rupture of the membranes in succeeding paragraphs. However, obstetric abnormalities or postmaturity necessitating admission prior to the onset of labor causes a high incidence of operative induction of labor so that the effect of this is shown by the increased percentage of patients of this type in the group with puerperal infection as contrasted with the normal one. It will be noted that this disparity exists in both the spontaneous and operative groups. It should be stated for purposes of clarity that induction by bag or bougie classifies the delivery as operative, while if the only manipulation is induction by artificial puncture of the membranes, the delivery is still classified as spontaneous. Referring again to Table V it will be seen that of the total cases analyzed similar numbers were admitted early in labor in both groups, whereas when the admission occurred late, more patients were found in the normal than in the infected series. However, if the groups

of spontaneous and operative deliveries are contrasted and only those patients admitted late in labor are considered, definite reversals of ratio occur. Thus, with spontaneous delivery, the preponderance of incidence is on the normal side and is 26.91 per cent as contrasted with 18.47 (infected group), whereas with operative delivery the reverse is found with 9.67 per cent in the normal and 19.33 per cent in the infected groups, respectively. No unequivocal explanation for these discordant findings is evident, although one might hazard the generalization that they indicate that if delivery is to be speedy and spontaneous, late admission to the hospital is without harm, while if some operative procedure will be necessary to terminate labor, it is of benefit to the patient to place herself under supervision as early as possible.

6. *Relation of Rupture of Membranes to Admission to the Hospital.*—Although it was impossible to determine any definite effect on the incidence of puerperal infection according to the duration of labor at the time of admission to the hospital a very definite correlation was found to exist when the time of admission was studied in terms of rupture of the membranes, and this is demonstrated in Table VI. Thus, when spon-

TABLE VI. PER CENT OF TOTAL CASES

	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
Before admission	21.03	7.01	20.45	5.62	20.48	7.66
After, spontaneous	45.02	61.30	28.03	51.68	40.00	58.06
After, artificial	33.95	31.68	51.52	42.70	39.52	34.27

taneous rupture of the membranes occurred prior to admission, the incidence of patients in the group of puerperal infection was three times as high as in the normal group when delivery was spontaneous and almost four times as high as when operative. Furthermore, this table shows that an increased rate of infection obtained when instrumental rupture was done after admission, which might indicate a hazard incident to this procedure when practiced after the onset of labor, although we have not found such to result when rupture was done to induce the process of parturition. From the two foregoing analyses it would seem that the duration of labor at the time of admission plays little rôle in the production of a subsequent infection, provided that hospitalization is accomplished prior to rupture of the membranes.

7. *Rupture of Membranes in Terms of Hours Before Delivery.*—Table VII indicates a rather direct correlation between the number of hours prior to delivery of rupture of the membranes and the incidence of puerperal infection. From this analysis a fairly sharp dividing line may be made at twelve hours, and providing not more than that time elapses between rupture of the membranes and delivery, the infection rate is not increased. However, when more than twelve hours elapse the inci-

dence of cases found is twice as high in the puerperal infection group as in the normal one; and, moreover, the mean time interval between rupture and delivery is much longer in the former than in the latter group, being seven hours two minutes and five hours twenty-two minutes, respectively.

TABLE VII. PER CENT OF TOTAL CASES

HOURS	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 2	66.57	70.47	47.61	57.95	61.09	67.92
3- 5	10.33	12.18	7.48	10.23	9.88	11.49
6-11	9.42	9.58	12.24	13.64	9.88	10.48
12-17	6.08	3.63	12.93	10.23	8.06	4.88
18-23	3.04	1.55	3.40	2.27	3.02	1.81
24 and over	4.56	2.59	16.33	5.68	8.06	3.42

8. *Cervical Dilatation at Time of Rupture of Membranes.*—The analysis of the rôle which early rupture of the membranes plays in the production of subsequent infection is concluded with Table VIII which

TABLE VIII. PER CENT OF TOTAL CASES

	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
Before labor	27.37	15.84	31.82	19.10	28.67	17.14
0-4 cm.	6.93	14.02	12.12	14.60	8.53	13.91
5-9 cm.	9.85	16.88	18.18	29.21	12.09	18.75
Fully dilated	55.84	53.26	37.88	37.09	50.71	50.20

indicates the effect of this factor in terms of cervical dilatation at the time of its occurrence. The main point of interest in this table lies in the incidence percentages noted when rupture occurred prior to the onset of pains with much higher figures obtaining in the infection groups throughout than in the normal ones. One may conclude that early rupture of the membranes, no matter at what stage of labor or before it, has little effect on the development of an ensuing puerperal infection providing delivery is consummated within twelve hours. It is not within the province of this report to discuss the debatable effect of premature rupture on the prolongation of labor, although this factor is, of course, important to the outcome of the individual case.

9. *Vaginal Examinations.*—It is a matter of Clinic policy that routine examination of the patient during labor be made per rectum and that vaginal touch be employed only when rectal findings are sufficiently unsatisfactory to warrant it. However, it is stipulated that with the exception of simple perineal forceps, a vaginal examination be done before any operative procedure is undertaken. Table IX is included to show the percentage of total patients in the series of whom vaginal examination (in most instances only one) was done, and it will be seen that with both spontaneous and operative delivery the incidence is almost

identical in the normal and infected groups. For the total patients with puerperal infection a considerably higher incidence of vaginal examination was noted than in the normal group, but this is chiefly due to the increased number of women in the former group who were delivered by operative means as contrasted with the latter series. The finding of a similar incidence of vaginal examinations in both infected and normal

TABLE IX

	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
Per cent of total cases examined	21.23	21.62	90.06	89.23	43.12	34.35

series with spontaneous delivery seems significant and, although rectal palpation undoubtedly constitutes a great advance in obstetric art, we feel that the above figures indicate that with proper surgical precautions vaginal examination does not necessarily materially increase the risk to the patient.

10. *Rectal Examinations.*—Table X indicates the number of rectal examinations made in the two series of cases under analysis and shows an increased number generally in the infected as contrasted with the normal group. Thus, the mean number of such examinations per patient

TABLE X. PER CENT OF TOTAL CASES

NUMBER OF RECTAL EXAMINATIONS	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 4	60.33	72.48	39.13	52.68	55.05	69.66
5- 9	31.56	23.59	33.54	32.26	31.38	24.43
10-19	4.47	3.44	20.50	11.83	8.99	4.96
20 and over	1.12	0.00	3.11	2.15	1.65	0.38
Unknown	2.51	0.49	3.73	1.07	2.94	0.57

with subsequent puerperal infection was 5.32 while for the normal group the lower figure of 3.97 was found. It is believed that this discrepancy is almost entirely to be explained in terms of a general prolongation of labor found in the infected series with a consequent increase of examining procedures.

11. *Duration of First Stage of Labor.*—The arbitrary time divisions noted in Table XI are employed in order to differentiate between precipitate labor (under three hours), normal labor (three to thirty hours), and prolonged labor (thirty hours and over). It will be observed that in multiparas a greater percentage of patients in the infection group had precipitate labors than in the normal series. No explanation seems evident for this finding other than that it is probably due to a sampling error since in the series of primiparas it does not hold good. This table

TABLE XI A. PRIMIPARAS. PER CENT OF TOTAL CASES

DURATION IN HOURS	F. T. S.		F. T. O.		TOTAL EXCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 2	5.91	4.83	0.00	5.17	3.94	4.90
3-29	85.03	87.92	73.23	79.31	81.10	86.04
30 and over	9.06	7.24	26.77	15.52	14.96	9.06
Mean duration	15 h. 24 m.	13 h. 59 m.	22 h. 48 m.	18 h. 12 m.	17 h. 52 m.	14 h. 55 m.

TABLE XI B. MULTIPARAS. PER CENT OF TOTAL CASES

DURATION IN HOURS	F. T. S.		F. T. O.		TOTAL EXCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 2	23.00	18.30	6.45	3.33	19.08	15.85
3-29	71.00	75.16	70.97	93.34	70.99	78.14
30 and over	6.00	6.54	22.58	3.33	9.92	6.01
Mean duration	11 h. 17 m.	10 h. 20 m.	21 h. 12 m.	11 h. 0 m.	13 h. 38 m.	10 h. 27 m.

illustrates clearly the increased incidence of prolonged labor and the greater mean duration of labor in patients subsequently developing infection as contrasted with those normal throughout the puerperium.

12. *Duration of Second Stage of Labor.*—It will be seen from Table XII that among both primiparas and multiparas the second stage of

TABLE XII A. PRIMIPARAS. PER CENT OF TOTAL CASES

DURATION IN MINUTES	F. T. S.		F. T. O.		TOTAL EXCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 59	69.29	73.56	42.61	41.38	60.68	66.54
60-119	27.80	22.60	32.17	44.83	29.21	27.44
120 and over	2.90	3.84	25.22	13.79	10.12	6.01
Mean duration	53 min.	48 min.	84 min.	74 min.	63 min.	54 min.

TABLE XII B. MULTIPARAS. PER CENT OF TOTAL CASES

DURATION IN MINUTES	F. T. S.		F. T. O.		TOTAL EXCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0- 59	93.18	88.23	61.91	73.33	87.16	85.79
60-119	6.82	9.80	23.81	16.67	10.09	10.93
120 and over	0.00	1.96	14.28	10.00	2.75	3.27
Mean duration	28 min.	29 min.	65 min.	45 min.	35 min.	31 min.

labor was found to be somewhat, but not significantly, prolonged in the infection groups as contrasted with the normal ones. The observed differences were very small in the series of spontaneous deliveries and rather more definite in the operative groups, although here the operative procedures themselves rather than the observed ten-minute difference in the mean duration of the second stage probably form the basis of the subsequent infections.

13. *Duration of Third Stage of Labor.*—Table XIII indicates that no difference was observed between the infected and normal groups with relation to the duration of the third stage of labor, and hence we feel

TABLE XIII. PER CENT OF TOTAL CASES

DURATION IN MINUTES	F. T. S.		F. T. O.		TOTAL EXCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0-14	85.67	89.16	73.29	73.11	81.82	86.17
15-29	13.20	9.85	19.88	20.43	15.28	11.82
30-59	0.84	0.98	4.35	5.38	1.93	1.80
60 and over	0.28	0.00	2.48	1.07	0.97	0.20
Mean duration	9 min.	9 min.	12 min.	13 min.	10 min.	10 min.

that it may be discarded as a factor in the production of puerperal morbidity unless operative procedures become necessary to terminate it or to control hemorrhage coincident to it.

Table XIV shows the mean total duration of labor in the two groups of patients with normal as contrasted with febrile puerperiums. It is interesting to note the discrepancy in the observed differences among the

TABLE XIV

	P. I.	NORMAL	DIFFERENCE
F. T. S., primiparas	16 hr. 26 min.	14 hr. 56 min.	1 hr. 30 min.
F. T. O., primiparas	24 hr. 24 min.	19 hr. 38 min.	4 hr. 26 min.
Total primiparas	19 hr. 5 min.	15 hr. 58 min.	3 hr. 7 min.
F. T. S., multiparas	11 hr. 54 min.	10 hr. 57 min.	0 hr. 57 min.
F. T. O., multiparas	22 hr. 29 min.	11 hr. 56 min.	10 hr. 33 min.
Total multiparas	14 hr. 23 min.	11 hr. 7 min.	3 hr. 16 min.

groups of spontaneous versus operative delivery and further emphasizes the already attested observation that prolonged labor and operative delivery affords an almost ideal combination for subsequent intrauterine infection.

15. *Tears, Perineal and Cervical.*—From a study of Table XV it would seem that perineal tears and episiotomies contribute but little to the etiology of puerperal infection, although in the group with spontaneous delivery episiotomy was performed about three times as often in the series with infected puerperiums as among the normal controls. However, including all degrees of tears, as well as episiotomy, it will be noted that some external perineal trauma occurred more frequently in the normal than in the infected series (spontaneous delivery alone). It

TABLE XV. PER CENT OF TOTAL CASES

TEAR	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
First degree	17.04	24.32	9.32	12.90	14.31	21.37
Second degree	12.85	16.71	26.71	6.45	16.33	14.12
Episiotomy	10.89	3.68	34.78	46.24	17.43	11.26
Third degree	0.84	1.23	1.86	0.00	1.10	0.95
Total	41.62	45.94	72.67	65.59	49.17	47.70
Cervical	1.12	0.00	9.32	6.45	3.67	1.14

is interesting to note that no significant difference was observed in the two series following third degree tears. However, with cervical lacerations the results were quite different and the incidence of such tears of sufficient degree to warrant repair was three times as great in those cases with puerperal infection as in the normal group.

16. *Postpartum Hemorrhage.*—That excess bleeding following delivery decreases the resistance of the patient and renders her more susceptible to subsequent infection is shown in Table XVI. The mean blood

TABLE XVI. PER CENT OF TOTAL CASES

BLEEDING	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
0-199 c.c.	46.63	58.02	18.30	24.73	39.33	52.68
200-399 c.c.	32.58	28.89	37.91	40.86	33.33	30.65
400-599 c.c.	11.52	7.90	30.07	34.41	16.67	12.45
600-999 c.c.	5.62	3.46	11.11	0.00	7.49	2.87
1000 c.c. and over	3.65	1.73	2.63	0.00	3.18	1.34
Mean blood loss	286 c.c.	229 c.c.	409 c.c.	317 c.c.	319 c.c.	243 c.c.

loss is consistently and significantly higher in the puerperal infection group as contrasted with the normal one. Moreover, the incidence of postpartum hemorrhage (600 c.c. or more) is two and one-half times as great in the abnormal as in the normal series. Although patients operatively delivered tend to bleed more than those with spontaneous termination of labor, yet the operative factor itself cannot be used to explain the above difference, since when only spontaneously delivered cases are considered the incidence of abnormal blood loss is almost twice as high in the infected group as in the normal one.

17. *Intrapartum Infection.*—The diagnosis of intrapartum infection was made whenever during labor and prior to delivery the mouth temperature rose to 100.4° F. or above and other causes for the febrile manifestation were ruled out. Table XVII indicates a frequency of

TABLE XVII. PER CENT OF TOTAL CASES

TEMPERATURE	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
100.4° F. or above	5.30	1.23	18.01	6.45	9.36	2.48

intrapartum infection between three and four times as great in the series of patients developing puerperal infection as compared with those who did not become infected.

18. *Intercurrent Disease.*—The analysis shown in Table XVIII was undertaken in an effort to determine to what extent intercurrent disease might play a rôle in increasing the probability of subsequent puerperal infection. From a comparison of the two series of infected and normal patients, it would seem that toxemia and cardiac disease had no effect.

TABLE XVIII. PER CENT OF TOTAL CASES

COMPLICATIONS	F. T. S.		F. T. O.		TOTAL INCLUDING PR.	
	P. I.	NORMAL	P. I.	NORMAL	P. I.	NORMAL
Toxemia	23.74	24.32	31.68	33.33	26.24	26.72
Syphilis	10.61	6.63	13.66	4.30	12.11	6.87
Pyelitis	6.15	0.49	9.94	0.00	6.97	0.38
Tuberculosis	1.68	0.49	0.62	0.00	1.28	0.38
Cardiac disease	0.56	0.74	1.86	0.00	0.92	0.57
Respiratory infection	1.12	0.24	3.11	0.00	1.83	0.19
Other	1.68	0.24	1.24	0.00	1.47	0.19
Total	45.54	33.15	62.11	37.63	50.82	35.30
Total without repeaters	39.11	31.94	47.20	37.63	42.02	33.97

However, syphilis, tuberculosis, and respiratory infection seemed definitely to enhance the probability of subsequent infection, as did pyelitis, although the relation between this complication and puerperal infection was obviously to be expected.

ANALYSIS OF GROUP WITH PUERPERAL INFECTION

1. *Days Postpartum at Onset of Fever.*—From Table XIX it will be seen that in five-sixths of the total patients, the puerperal infection began to manifest itself in terms of a febrile reaction (100.4° F. or above)

TABLE XIX. PER CENT OF TOTAL CASES

DAYS	F. T. S.	F. T. O.	TOTAL INCLUDING PR.
1	20.95	32.30	24.77
2	20.95	25.47	22.39
3	20.39	13.04	18.90
4	21.23	11.80	17.80
5	5.03	7.45	5.50
6	6.15	3.73	5.32
7 and over	5.31	6.21	5.32
Mean number days	3.16	2.80	3.01

in the first four days after delivery. Almost a fourth of the cases became febrile in the first twenty-four hours, which in our opinion is too short a time for an infection attained at the time of delivery to become evident clinically. In only about 5 per cent did a week or more elapse before the febrile reaction occurred, and it is our opinion that in the majority of these cases the infection was gonococcal in origin, this opinion being frequently confirmed by cervical smear although culture reports were usually negative for this organism. The mean number of days elapsing between delivery and the onset of infection was three, and there seemed to be a tendency for clinical signs to occur somewhat later in spontaneously delivered as contrasted with operatively delivered patients.

2. *Duration of Fever.*—It will be noted from Table XX that approximately one-fourth of the cases of clinical puerperal infection have a

febrile phase of only two days, and half of the total three days, while only an eighth have a duration of a week or more. This indicates that in the vast majority of cases the infection is mild and does not progress

TABLE XX. PER CENT OF TOTAL CASES

DAYS	F. T. S.	F. T. O.	TOTAL INCLUDING PR.
2	28.21	19.25	25.14
3	26.54	21.74	24.95
4	14.25	15.53	14.86
5	10.34	11.80	11.19
6- 7	10.34	11.18	10.46
8-15	7.55	16.15	10.09
16-30	2.24	4.35	2.94
31 and over	0.56	0.00	0.37
Mean number days	4.39	5.43	4.73

past the stage of endometritis. Those cases following operative delivery tend to have a longer duration than when labor terminates spontaneously, with the mean duration for the entire series being 4.73 days.

3. *Height of Fever.*—Table XXI is included in order to demonstrate the general degree of severity of the cases in the series in terms of amount of fever, the highest temperature reading being taken as the

TABLE XXI

FEVER	F. T. S.	F. T. O.	TOTAL INCLUDING PR.
100.4-100.9	15.08	14.29	14.50
101 -102.9	60.34	58.39	60.37
103 -104.9	22.35	23.60	22.20
105 and over	2.23	3.72	2.93
Mean elevation	102.1	102.3	102.2

index. It will be noted that in only one-fourth of the total patients did the fever reach 103° F. while in less than 3 per cent of them was the high reading of 105° F. attained.

In passing, it may be said that mathematical correlations were done in an effort to determine what relation, if any, existed between the above three factors which have been discussed. It was found that no correlation existed between the time of onset of fever and its severity as judged by the highest temperature reached. There was a slight but not significant relation between the time of onset of fever and its duration. A marked and significant correlation was adduced between the height of fever and its duration. From these figures one may imply that the time of onset of fever in the puerperium gives no indication as to the clinical severity which the individual case may attain, although naturally the degree of febrile reaction is sharply significant.

4. *Organisms Found in Intrauterine Culture.*—After two febrile days an intrauterine culture was obtained by means of the "Little" tube on 60 per cent of the patients in the series, and in this way the bacterial

content of the lochia was studied. Table XXII indicates the results obtained according to the type of organism involved. It will be noted that despite clinical indications of intrauterine infection the report in 12 per cent of the total was either "diphtheroids alone" or "no growth." It is our feeling that better technic in carrying out the anaerobic studies would reduce these two groups to a considerable extent. The hemolytic streptococcus was present in 5 per cent of the cultures obtained from patients delivered spontaneously and 7 per cent in operative deliveries,

TABLE XXII. PER CENT OF TOTAL CULTURES

ORGANISM	F. T. S.	F. T. O.	TOTAL INCLUDING PR.
α hemol. strep.	0.91	2.35	1.23
β hemol. strep.	4.09	4.71	4.92
Aerobic nonhemol. strep.	17.73	31.76	21.54
Anaerobic strep.	52.27	36.67	47.69
Strep. viridans	0.00	1.18	0.31
Staph. albus	27.73	31.76	28.62
Staph. aureus	0.91	1.18	0.92
B. coli	4.55	9.41	5.54
Gonococcus	1.36	0.00	1.23
B. welchii	0.45	1.18	0.62
Unidentified bacteria alone	0.45	1.18	0.62
Diphtheroids alone	5.45	3.53	4.92
No growth	7.73	5.88	7.08

while some type of streptococcus was found in 75 per cent of the total cultures. It is interesting to note the higher incidence of aerobic nonhemolytic streptococci and also *B. coli* in the group of operative deliveries as contrasted with spontaneous. No particular effort was made to culture the gonococcus, which accounts for the low incidence of this organism.

5. *Some Differences Observed Between Infections with the Hemolytic, Aerobic Nonhemolytic, and Anaerobic Streptococcus.*—Table XXIII is included in order to demonstrate certain essential differences in the cases of puerperal infection according to the type of streptococcus involved. It will be seen that a marked racial difference existed. Three-fifths of the hemolytic streptococcus infections occurred among white patients, while only one-third and one-quarter of the cases due to the aerobic nonhemolytic and anaerobic streptococcus, respectively, were in the white

TABLE XXIII

ITEM	HEMOLYTIC STREP.	AEROBIC NONHEMOL. STREP.	ANAEROBIC STREP.	TOTAL INFECTION SERIES	TOTAL NORMAL SERIES
White	60.00%	33.87%	25.00%	38.40%	53.60%
Black	40.00	66.13	75.00	61.60	46.40
Primiparas	65.00	75.81	68.24	72.66	55.36
Multiparas	35.00	24.19	31.76	27.34	44.64
Mortality	10.00	0.00	1.35	1.28	0.00
Spontaneous	65.00	66.13	79.73	68.99	80.72
Operative	35.00	33.87	20.27	31.01	19.28

group. If one considers the hemolytic streptococcus cases as the most typical group of direct contact infections (by the physician or nurse) the figures adduced agree fairly well with the racial admixture observed in the normal series (53.60 and 46.40 per cent white and black, respectively). The incidence of infections due to the anaerobic streptococcus according to the type of delivery approximates much more closely the make-up of the normal than of the infected series. No significant alterations according to type of organism were noted with the parity of the patients. There were seven deaths in the group of 545 cases of infection, a mortality rate of 1.28 per cent, and, as was to be expected, most of these (4) occurred in the hemolytic streptococcus group. One of these deaths was due to pulmonary embolism but the remainder were definitely caused by the infectious process (septicemia 3, peritonitis 2, and thrombophlebitis 1).

As a final analysis, it was deemed of interest to ascertain the number of instances of infection in the series which were unaccompanied by any external predisposing factor. These were cases with spontaneous delivery, and without vaginal examinations, perineal or cervical lacerations, premature rupture of membranes, prolonged labor or postpartum hemorrhage. It was found that one-fourth of the cases in the series fell into such a group, 30.29 per cent of the total blacks and 18.05 per cent of the total whites, respectively. In two-thirds of this group the anaerobic streptococcus was the infecting organism. The causes of the intrauterine process in these 140 patients must remain a matter of conjecture. Undoubtedly, in a number of these and particularly in the colored race, the patient herself was at fault through self-manipulation during labor, while in others intercourse just prior to the onset of labor might well be blamed. Probably some were gonococcal in origin while others represent a blood-borne infection from some disease focus elsewhere in the body. It seems reasonable to suppose that many represent infection attained by organisms from the nasal spray of the patient or of some attendant at labor or delivery. One can merely surmise as to the possibility of these cases of clinical puerperal infection being instances of autogenous infection, since recent studies have cast considerable doubt upon the possibility of this happening. It is, however, of interest that one-fourth of the total cases analyzed comprise a group that in the light of our present knowledge must be classed as unpreventable. Most of this group, fortunately, were clinically mild in character, and there were no deaths occurring among them.

SUMMARY AND CONCLUSIONS

A detailed analysis and comparison has been made of two series of patients delivered at or near term on the Obstetrical Service of the Johns Hopkins Hospital, divided according to whether the puerperium was normal or febrile due to puerperal infection. Instances of cesarean

section have been omitted. The purpose of the comparison was to elicit factors in the patient and her labor which would seem to predispose toward the development of a subsequent intrauterine infection. The following are some of the factors adduced:

1. The incidence of operatively delivered patients was much higher in the group with puerperal infection than in the normal series.

2. Puerperal infection occurs much more frequently in black than in white women, and this difference is significantly greater with spontaneous than with operative delivery.

3. Women in the earlier years of their childbearing careers, and also primiparas, are more predisposed to intrauterine infection than those of the older age groups and multiparas.

4. The time of admission to the hospital in terms of duration of labor seemed to play no part in a subsequent infective process.

5. The incidence of rupture of the membranes prior to admission to the hospital was almost three times as high in the group of patients who later developed a puerperal infection as contrasted with those whose subsequent course was normal. Rupture of the membranes occurring more than twelve hours before delivery seemed definitely to predispose the patient to infection, and our analysis indicated that premature rupture of the membranes either before the onset of pains or early in labor was of little import provided delivery was consummated within the above time period.

6. Vaginal examination, as employed whenever necessary to corroborate or amplify rectal findings, carried no added danger to the patient.

7. The duration of labor, both in primiparas and multiparas, in terms of the first and second stages, was significantly longer in the group of infected patients as contrasted with the normal puerperium series. Depending upon parity and type of delivery the mean duration in the two groups varied from one to ten and one-half hours and was persistently higher in the infection series.

8. The incidence of perineal tears or episiotomies was slightly higher in the infected group, but the number of cervical lacerations of sufficient extent to warrant immediate repair was three times as great.

9. The amount of blood lost subsequent to delivery was significantly greater in the infected as contrasted with the normal group and the incidence of postpartum hemorrhage (600 c.c. or more) 10.67 and 4.21 per cent for the two series, respectively.

10. Intrapartum infection (temperature during labor 100.4° F. or above) was observed almost four times as frequently in the infected as in the normal group.

11. Intercurrent disease, particularly syphilis, pyelitis, and respiratory infection, was a complicating factor much oftener in those patients with subsequent intrauterine infection.

12. The mean number of days between delivery and the onset of infection in terms of a rise in temperature to 100.4° F. or above was three, and in 84 per cent of the cases the onset was during the first four days.

13. The average duration of fever was 4.73 days and was longer in those patients with operative than in those with spontaneous delivery. In 86 per cent of the patients the febrile manifestation had disappeared within seven days.

14. The mean highest temperature noted during the infective process was 102.2° F. and in less than a quarter of the total group did the fever attain a reading of 103.0° F.

15. Intrauterine cultures were done in over 60 per cent of the patients in the group and some variety of streptococcus was obtained in over three-fourths of them, although the incidence of *S. hemolyticus* was only 6 per cent. A higher percentage of anaerobic streptococcus was found in spontaneous than in operative deliveries, while reverse proportions occurred for the aerobic nonhemolytic streptococcus. The colon bacillus was found twice as often following operative as after spontaneous deliveries.

16. For the total series of cases of puerperal infection 38.4 per cent were in white and 61.6 per cent were in black patients. In contrast to this, 60 per cent of the infections due to the hemolytic streptococcus were in white women, whereas only one-third and one-fourth of the groups due to the aerobic nonhemolytic and anaerobic streptococcus, respectively, were in this race. The division of the cases due to the anaerobic streptococcus, according to whether delivery was spontaneous or operative, tends to approximate closely a similar division of the group with normal puerperium; while the hemolytic and aerobic nonhemolytic varieties approach more closely the infected group. The total maternal mortality was 1.28 per cent and the majority of deaths were due to the hemolytic streptococcus.

17. In more than one-fourth of the total cases of the series the labor and delivery had been normal and without any intravaginal manipulation. This large group of cases were all spontaneously delivered, the membranes had not ruptured spontaneously, labor was not prolonged, there were no vaginal examinations, no laceration occurred to perineum or cervix, and bleeding after delivery was not excessive. Many of these patients were probably self-infected, by digital manipulation during labor, by intercourse shortly before or during the early hours of labor, or through the blood stream from a focus of infection elsewhere in the body. Some were probably gonococcal in origin. Others were undoubtedly due to streptococci from the nasal spray of some attendant at delivery or the patient herself. One cannot definitely state that any of these cases were instances of autogenous infection but it seems significant that of a large group of patients with puerperal infection more than a quarter must be classed as unpreventable in view of present obstetric knowledge.

DÜHRSSEN'S INCISIONS

An Analysis of 592 Cases

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ONE of the most trying dilemmas encountered in obstetric practice is with the patient, who after many hours of active labor, presents urgent indications for delivery but presents an incomplete dilatation of the cervix. Cesarean section usually is not merited because there is no actual bony disproportion or is contraindicated by frank or potential infection.

Manual dilatation of the rigid cervix now is branded as "manual tearing" and is condemned because of dangers of trauma and hemorrhage with morbidity both immediate and remote. Dührssen's incisions constitute a clean surgical procedure and would reasonably be expected to lessen these hazards.

Dührssen,[1] who first put cervical incisions during labor on a sound basis as an operative entity, performed his first operation on Nov. 10, 1887. He readily granted priority for the procedure of incising the cervix,[2, 3] but justly insisted on the originality of his practice of making multiple deep incisions to the vaginal fornix, and virtually effecting the conditions of complete dilatation by surgical means. Many of the earlier writers allude to the use of this incision as a last resort.[4-9] Launergat[1] and Skutsch[10] (1887) made more extensive use of it.

The use of clamps (Zweifel), broad retraction (DeLee), incision at points in the cervix corresponding to 10, 2, and 6 on the clock, and careful suture of the incisions constitute technical improvements. Cervical dystocia in the elderly primiparas rather than eclampsia was Dührssen's earlier indication but eclampsia was later his prime indication; weak pains were not an indication. Careful asepsis and all the benefits of a complete maternity hospital and an emphatic warning against a careless conscience in its usage was urged.

Dührssen's series[1] of 31 cases was the largest published until Shir[16] reported 162 cases. Olow,[11] Cathala,[12] Roscal,[13] Mathieu and Schauffler,[14] Randall,[15] and others have commented on the procedure and reported small, scattered series of cases in the last two decades.

Five hundred and ninety-two cases in which Dührssen's incisions were done, occurred at the Chicago Lying-In Hospital from 1917 until November, 1932, during which time slightly less than 40,000 confinements are recorded. Thus the incidence of the operations is 1.48 per cent. This incidence is high, but it was promoted by the ideas of forestalling serious effects of marked maternal exhaustion and the preservation of the fetus,

many of which were those of relatively infertile elderly primiparas. One hundred and thirty-seven cases gave evidence of fetal distress. Prolonged labor was the rule. Over one-third of the patients had abnormal pelves and 11.5 per cent were of the troublesome "dystocia dystrophy syndrome" category. Many patients were constitutionally below par, inertia was common, dozens started in labor unsatisfactorily and yet did not present definite indications for cesarean section at the outset. In evaluating the merits of this record one must never lose sight of the fact that the majority of these cases could, without exaggeration, be classified as the most difficult and trying of the series of 40,000. As further evidence of this fact a large number of patients presented several complications any one of which would cause concern to an experienced obstetrician.

During the year (Oct. 1, 1932, to Oct. 1, 1933) the incidence of Dührssen's incisions dropped to 1 per cent, or 28, in 2,808 deliveries, due, perhaps, to better treatment of the prolonged first stage and possibly to extension of the use of cesarean section.

In general, an indication arises when danger is present or imminent to mother or child unless delivery is rapidly effected.

Maternal indications include:

1. Severe exhaustion in spite of treatment when, after a prolonged labor, progress has been arrested for several hours. Cervical dystocia may arise if a tough, resistant cervix be present. There may be faulty pains which cannot produce proper dilatation. "Transverse arrest" may complicate the mechanism of labor.

2. Serious preeclampsia or eclampsia in the face of slow progress and unsatisfactory medical treatment is occasionally an indication.

3. Cardiac decompensation during labor is an excellent indication if the patient can be delivered by Dührssen's incisions and a not too difficult forceps operation.

4. A true Bandl's ring with or without uterine tetany may bring labor to a standstill and threaten the baby or mother or both. If relaxation cannot be obtained by anesthesia, a trial of adrenalin, etc., cervical incisions may be indicated. This was the sole indication in eight and was combined with others in twenty-six cases.

5. Any sudden exigency such as abruptio placentae with sudden concealed or external bleeding when labor is well advanced. Live babies were secured in three cases of abruptio placentae.

Fetal indications include prolapsed cord, marked and progressive irregularity of the fetal heart sounds or the passage of meconium in cephalic presentations.

Contraindications.—Placenta previa is an absolute contraindication for Dührssen's incisions. This condition was the sole indication in two patients with serious hemorrhage. It was also a secondary indication three times. One should always endeavor to keep the friable and extremely vascular lower uterine segment intact. Incisions into this field wherein extensions by tearing may involve the enormous uterine sinuses is a folly that may invite a dangerous or even fatal hemorrhage.

The patient should have received the advantage of proper supportive treatment in the first stage of labor. The uterus regains strength, effective pains return, and the cervix dilates spontaneously in many cases of prolonged labor with proper administration of food, fluids, and rest. This course is always to be preferred to operative means, all things being equal. Forty per cent of patients in this series did not receive a sedative hypodermic and of the remaining 60 only 20 received more than one. Such supportive therapy should logically be a part of what is called watchful or "intelligent" expectancy. Intelligent expectancy is by no means synonymous with hopeful procrastination. A normal spontaneous delivery often occurs or at least a less dangerous operative one becomes possible after such management.

Supportive therapy during the first stage should not be so delayed that the patient's condition will not permit of trial. The patient cannot be safely left in labor without the benefit of foods, fluids, and rest. Obviously all cases are not solved by administering fluids and rest; if dehydration and exhaustion with perhaps fever and a rapid pulse develop after thirty-six or forty-eight hours of labor, operative methods are usually soon required.

One must also make certain that the patient is really in active labor. As Horner [17] states, "Even after long observation of the patient one may be deceived. It is often difficult to denote the time of transition from false into true labor pains." Regularity of the contractions of adequate strength and duration with progressive dilatation of the cervix are about the only criteria of active labor.

Persistence in inducing labor with a long, closed, firm, stubborn cervix before it has become softened and partially effaced almost invariably results in a long troublesome labor before complete dilatation is finally reached. Operative deliveries often follow such a course whereas if the patient has been treated with a sedative she might return to the hospital in a day or week in spontaneous active labor and deliver normally with relative ease. This contention is supported by the fact that 16.4 per cent of these patients received mechanical induction as compared to an incidence of 3.8 per cent during the past year for all cases, an incidence four times as high. Possibly some of these patients might better be subjected to laparotrachelotomy where the indication for termination is urgent. This applies especially to those with some appreciable pelvic disproportion, the membranes not too long ruptured, the patient not potentially infected. The woman runs a slightly higher risk, possibly, but the genital tract is not so severely or permanently traumatized and the baby's outlook is immeasurably better than after a difficult forceps operation.

Last, in placing the indication for Dührssen's incisions, as in all surgical procedures, the individual case should be pondered carefully. One

should enter into the procedure with at least as much forethought as with cesarean section or other major obstetric operations.

A prolonged first stage of labor without progress for more than eight hours in spite of previous supportive therapy probably demands treatment by incisions when the contractions have been moderately severe and the cervix is in proper condition. After a thorough study of this large series of cases we cannot but coincide with Dr. F. L. Adair's[18] views on the indications and conditions for the operation, namely:

> Dührssen's incisions are permissible only in those cases where prompt termination of labor is necessary, either in the interest of the fetus, the mother, or both. The cervix must be adequately effaced, though it is improperly dilated, and conditions must be such that the subsequent operation for delivery would be indicated and could be properly performed if the cervix were already fully effaced and dilated.
>
> It is an operation for specially trained practitioners, to be carried out only in a suitable environment as a well-equipped maternity hospital.

TECHNIC

As most patients are primiparas, and adequate exposure is essential, a deep mediolateral episiotomy is made. Because of the depth of the episiotomy and the long labor, hemorrhage from the episiotomy may be profuse. It must be quickly and effectively controlled, by a gauze pack against which pressure is exerted by the vaginal retractor.

Control of blood loss from the perineal and cervical incisions is of the highest importance, because postpartum hemorrhage and infection are more prone to occur in these patients in whom the labor is prolonged and the operative manipulation excessive. It may be feasible to tie two or three of the larger bleeders in the episiotomy wound, but valuable time and blood should not be lost in being too exacting in this as the pack should prove sufficiently effective.

With adequate exposure the cervix may be clamped posteriorly and pulled down gently for this incision. The posterior incision is made first because, if done after the anterior ones, the bleeding from them tends to obscure the field. Long-handled clamps and scissors facilitate the operation. Neither should have sharp points. It may be necessary to pull down gently on the clamps to expose more adequately the cervix before finally placing them, but one should remember that the cervix may be friable (especially if edematous) and a tear may be dangerous. Under sight and palpation the incisions are made between the clamps *to the fornix* (Fig. 1). In many cases clamps are entirely unnecessary. If, as rarely happens, one cannot cut entirely to the fornix with the certainty of not injuring the bladder, rectum, or peritoneal cavity, cut only as far as is safe on palpation and sight. Deliberate delivery is rewarded by less likelihood of extension of the incisions.

After delivery of the child and placenta, the retractors are replaced and the edges of the cervix are grasped with sponge forceps for inspection and for repair. If the patient is in shock or bleeding too profusely for repair, the lower uterine segment and vagina can be packed tightly to control the hemorrhage, and the cervical wounds left for later repair. Similarly, if there is evidence of frank genital infection such as chills and high fever or purulent discharge, repair is strongly contraindicated.

Rupture of the lower uterine segment should not be overlooked, though none serious enough to warrant hysterectomy occurred in this series. It is surprising how well these unrepaired incisions often heal. In event of an extension of the incision, Allis clamps placed high on the edges of the wound may expose the apex or a traction suture high in the wound may facilitate the closing of the top portion of the extension.

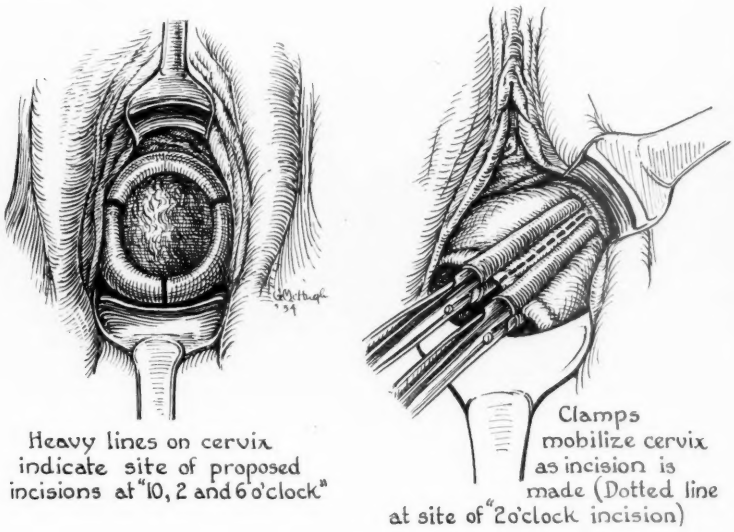
Heavy lines on cervix indicate site of proposed incisions at "10, 2 and 6 o'clock"
Clamps mobilize cervix as incision is made (Dotted line at site of "2 o'clock incision)

Fig. 1.

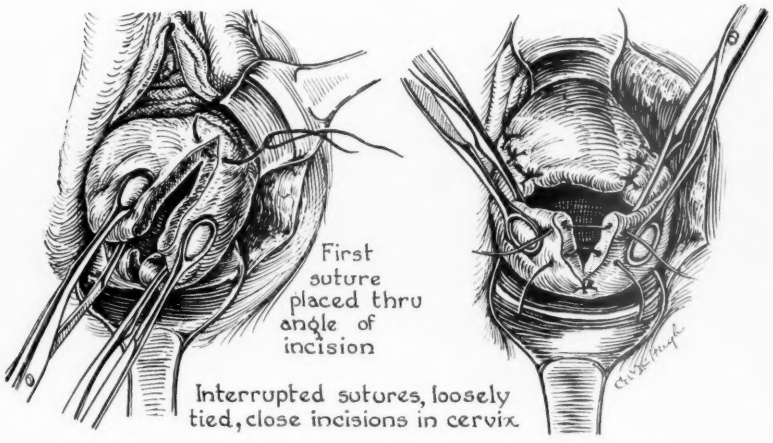

Fig. 2.

Care should be taken to evert the tissue at the upper angle of the wound or poor union will result.[19] Two to four sutures of number two, twenty-day, chromic catgut are used to carefully approximate each wound, avoiding the endocervix (Fig. 2).

Speed in the repair of the cervical incisions and episiotomy wound is imperative not only to save blood, but also because the patient has undergone a long labor and an operative delivery with prolonged anesthesia.

The Dührssen's operation may be done under local parasacral anesthesia, if indicated.[20]

REVIEW OF CASES

Age.—The age varied from seventeen to forty-four with an average of 26.7 years which is above the average age in this clinic, especially as the vast majority were primiparas.

Bodily Build.—The height and weight (an attempt to evaluate stature) showed no deviation from the normal for women of this age.

Parity.—Obviously one would expect cervical dystocia from rigidity to be an affliction of primiparas, and this series bears this out, 88.7 per cent being primiparas. Fetal indications predominated in the multiparous cases.

Duration of Pregnancy.—A study of the duration of pregnancy in weeks gives some evidence of the increased incidence of postmaturity in these cases. Roughly, one-fourth of the cases were premature, slightly over one-third at term, and one-third postmature. The weights of the babies tend to substantiate the postmaturity of these pregnancies.

Pelvis.—Pelvic dystocia was present in many cases and may have been a factor in the prevalent cervical dystocia by not permitting the head properly to fit the cervix from failure of proper engagement. The frequency of occiput posterior positions may be, in fact, accounted for by this incidence of contracted pelvis. And yet in 377 cases or 63.8 per cent the pelvis was classified as normal or justo-major from careful prenatal measurements often checked again during labor or at delivery.

Sixty-eight cases, or 11.5 per cent, were of the dystocia, dystrophy syndrome, or achondroplasia group. They include the short, stocky, masculine type of woman so adequately described by Horner and DeLee.[10]

Induction.—Of 536 recorded cases, 105 were induced, 88 mechanically, and 17 medically, a ratio of 1 to 5, far above the usual incidence of induction. One would be led to believe that the long-drawn-out labor commonly seen from the forced induction with an "unripe" cervix may be one factor in producing cervical dystocia.

While *uterine inertia* played a rôle in these cases of dystocia, it cannot be compared with cervical dystocia and exhaustion as an etiologic factor. Weak pains were observed in less than one-fourth of the cases.

Comments on the state of the cervix, aside from degree of effacement and dilatation, were rare, yet in 83 there was a marked edema and in 30 a remarkable rigidity was noted. The variance of cervical dilatation is worthy of note and yet 80 per cent of the cases attained a dilatation of 7 cm. or more.

Length of Labor.—Obviously labor was prolonged except where sudden fetal or maternal indications arose with conditions favorable for delivery from below. It would have been foolhardy to have allowed these women to labor for days in the face of no progress after twelve to eighteen hours. In fact, as experience was gained in observing this type of prolonged labor, a more radical attitude was often taken by performing the incisions after a shorter period of failure to progress. As a result, many cases were better risks than after a low grade fever with tachycardia had developed with signs of exhaustion. In the opinion of many of the operators the incidence of infection and general morbidity was also thus reduced.

The average duration for the entire series was 33.6 hours: for 64 multiparas, 18.9 hours; for 525 primiparas, 35.4 hours, considerably over the average figures given in the standard textbooks. Sixty-one per cent of the patients labored over twenty-five hours and 20.3 per cent over fifty hours.

The incidence of prolonged labor (over twenty-four hours) at the Chicago Lying-In Hospital in the past year (Oct. 1, 1932, to Oct. 1, 1933) was 264 cases in 2,808, or 9.4 per cent, as compared with 61.1 per cent in this series. *Therefore it is noted that prolonged labors are increased sixfold over normal incidence in these cases.*

The average duration of ruptured membranes was 19.5 hours.

Presentation and Position.—It must be stressed that the diagnosis of position and presentation was made vaginally in each instance and checked at delivery and therefore furnishes accurate data. It represents a fairly large series of obstetric cases wherein the diagnosis is surely known.

Only 16.9 per cent were occipitoanterior, 31.4 per cent were occipitotransverse and 48.8 per cent, or nearly one-half, were occipitoposterior positions. If the occipitoanterior position is considered as normal, then 83 per cent of these cases had an abnormal position. Thirty-four breech presentations were encountered, a percentage of 5.8 per cent, or nearly twice the normal incidence.

Indications.—General indications for Dührssen's incisions have already been discussed (Table I). As labor drags on further and further beyond the length that has been called average, a multiplicity of untoward findings are likely to appear, often suddenly. Thus in this series it very frequently occurred that more than one indication arose; for example, in 152 cases there was a combined fetal and maternal indication mentioned.

It is interesting to note that there was dystocia from the scars of previous Dührssen's incisions in only two cases of this series.

Number of Incisions and Extensions.—Three incisions should be distinctly preferred as a prophylaxis against either extension of incisions or lacerations during the instrumental delivery which usually followed the incisions. Consequently, a correlation was made between the incidence of cervical lacerations or extensions

TABLE I

Fetal Indications:		
Irregular or failing F. H. T.		137
Meconium in cephalic present		40
Prolapsed cord		25
Malposition of fetus (Maternal or not listed)		5
		211
Maternal Indications:	COMBINED	ALONE
Exhaustion	206	104
No progress	196	93
Cervical dystocia	115	46
Preeclampsia	49	23
Uterine inertia	26	15
Transverse arrest	18	6
Progressive edema	19	6
Eclampsia	15	12
Cardiac decompensation	11	0
Tetanic uterus	5	2
Bandl's ring	21	6
Persistent occiput posterior	4	3
Placenta previa	3	2
Abruptio placentae	3	0
Fetal indications combined with maternal ind.	152	
Fibroids		4
Toxic thyroid		4
Vaginal bleeding (undiagnosed)		3
Anterior parietal presentation		4
Face presentation		3
Previous cesarean section		3
Previous Dührssen's incisions		2
Previous anterior suspension		1
Brow presentation		1
Uterine prolapse		1
Uremic or eclamptic coma		1
Severe vomiting five days with acidosis		1
Acute psychosis		1

and the number of incisions with the results that there were almost exactly the same number of accidents of this sort whether two or three incisions were made. If only one incision was made there was a slightly greater chance for extension by tears. However, when only one incision was made the dilatation was nearly complete. Perhaps the more serious extensions and lacerations might have been eliminated with three incisions. If the cervical dilatation is far from complete three incisions are much safer.

Delivery.—Incision was invariably followed by delivery. Forceps were applied as a rule although 66 versions were performed. Forceps delivery failed in 21 instances, delivery being effected by version or craniotomy, depending on fetal viability at the time the forceps failed. The disastrous effects of high and the more difficult midforceps on the fetus is mentioned below and accounts for about one-half of the rather high fetal mortality. Rotation of the fetal head in the cases recorded could be accomplished manually in 204 instances while forceps rotation was required 106 times.

Weight of Babies.—While the average length (49.9 cm.) and weight (3,330 grams) of the babies is only slightly, if any, over the average, the number of babies over the average weight is relatively high. Only 143 babies weighed less than 3,000 gm. while 405 were over that figure and 218 weighed over 3,500 gm. The higher percentage of heavier babies linked with the number of overterm pregnancies establishes oversize as a real cause of the type of dystocia under consideration. The harder postmature fetal heads are notoriously deficient in their ability to mold readily into the pelvis and fit against the cervix firmly.

Postpartum Hemorrhage and Pathologic Third Stage.—A study of the blood loss and difficulties of the third stage of labor reveals much of interest in these cases. The fear of hemorrhage following this radical procedure voiced by both the older and present-day obstetricians is well founded.

The blood loss was estimated in 570 cases. Of these 161, or 28.8 per cent, lost over 500 c.c. which figure is arbitrarily taken to mean a postpartum hemorrhage. The average for all cases was 398 c.c. These are only estimates; if accurate measurements had been taken, the average would probably have been greater.

A separate analysis of the first and last 100 cases gives some striking information relative to blood loss. The average blood loss for the first 100 patients was 539 c.c. with 50 patients losing 500 c.c. or more. Thus, exactly one-half of the first 100 patients had a postpartum hemorrhage according to our standard. In the last 100 patients the average blood loss was only 310 c.c., *an average reduction per patient* of 229 c.c. Only 14 per cent lost 500 c.c. or over.

Several factors account for this improvement. Perhaps the most important one was the realization that controlled and even radical management of hemorrhage, if required, was a conservative course to follow, after one has embarked on such a radical procedure in patients who are not in ideal condition after a long exhaustive labor. A glance at the morbidity table below will show that postpartum hemorrhage was more frequently correlated with a febrile puerperium than was any other factor including even the various types of intrauterine manipulation.

Recent use of intravenous pituitrin in the early stage of hemorrhage from uterine atony may have helped avoid more serious hemorrhages. A more alert regard for small but steady blood loss from a bleeding episiotomy wound or cervical wounds has saved much valuable blood. The insidious "drip" from the edge of the towel under the patient's buttocks may accumulate into a serious hemorrhage in the course of a long operative delivery. Any bleeding wound should be compressed where possible. This may save 200 to 300 c.c. of blood in a long delivery and help overcome later morbidity.

Intravenous infusions of glucose or acacia solution on occasion, hypodermoclysis and blood transfusions, while seldom needed might have been employed more fre-

quently. For the last several years this has been the practice when indicated and is one reason for the greatly improved mortality statistics in the last half of this series.

Many of these patients were, theoretically at least, candidates for postpartum hemorrhage by virtue of such so-called predisposing factors as long labor, deep anesthesia, large babies, etc. Radical management of the third stage was often necessary. The placenta was delivered spontaneously by external pressure in 311 cases, but 125 placentas were manually removed, many incidental to manual exploration of the genital tract to detect or rule out serious damage to maternal soft parts, such as rupture of the lower uterine segment. Uterine tamponade was employed thirty-seven times. Facts relevant to hemorrhage are seen in Table II.

TABLE II

Entire Series—570 Cases		
Average blood loss	389 c.c.	
500 c.c. or over	161 Cases	28.2%
First 100 Cases		
Average blood loss	539 c.c.	
500 c.c. or over	50 Cases	50.0%
Last 100 Cases		
Average blood loss	310 c.c.	
500 c.c. or over	14 Cases	14.0%

Correlation of Thickness of Cervix to Blood Loss.—It was an especial point of interest to prove or refute the universally expressed idea that incision of a thick cervix invites dangerous hemorrhage. A review of the cases revealed that the blood loss was only slightly in excess in the cases of thick cervix, compared with those cases where the cervix was thin or well-effaced. The average blood loss for both groups was less than in the total series. Greater blood loss was incurred from incising an edematous cervix, as a tabulation of hemorrhage from seventy-nine cases with edema of the cervix showed an average blood loss of 407 c.c. (Table III).

TABLE III. CORRELATION OF THICKNESS OF CERVIX TO BLOOD LOSS

Average blood loss for 570 cases	389 c.c.
Average blood loss 367 cases with "thin" cervix	372 c.c.
Average blood loss 93 cases with "thick" cervix	383 c.c.
Average blood loss for 79 cases of edematous cervix	407 c.c.

Morbidity.—From the nature of these cases one could predict an unfavorable incidence of morbidity. Over one-half of the patients (51.4 per cent) showed a febrile morbidity of 100° or more (DeLee), 23.2 per cent by the British Standard, and 14 per cent by the Strassburg Standard. Table IV shows an effort to correlate etiology with morbidity. It is obviously often difficult to point out a tangible cause for infection in most of these cases. Therefore two tables of morbidity were compiled; one wherein there was a sole probable etiologic and another where there was a combination of one or more possible etiologic factors. Postpartum hemorrhage was the greatest single offender. It is of especial significance to emphasize that not a single death occurred from sepsis. One patient who died of abruptio placentae immediately after delivery had an intrapartum temperature with one chill.

Table V compares the morbidity of these cases with 2,808 consecutive cases in the hospital for one year, and also with 148 cases of delivery subsequent to Dührssen's incisions.

The immediate fetal morbidity was high but usually not serious if condition at discharge from the hospital is taken as the criterion. There were injuries such as scalp and facial bruises, facial palsy, deep forceps marks, and "asphyxia," but they were almost universally transient.

TABLE IV. MORBIDITY

	DE LEE COMBINED	STANDARD ALONE	BRITISH COMBINED	BRITISH ALONE	STRASSBURG COMBINED	STRASSBURG ALONE
Total cases		304		137		83
Manual dilatation	5	1	3	1	4	0
Intrapart. temp.	27	5	11	1	11	2
Version	34	14	20	7	13	4
Uterine pack	36	1	24	2	18	0
Ruptured B.O.W.	68	19	30	7	17	2
Bag or gauze	75	19	38	9	25	5
No cause		80		25		17
Manual removal	83	24	39	5	27	3
P.P. hemorrhage	104	31	55	14	31	9

Other possible causes:	
Pyelitis	6
Thrombophlebitis	4
Infected perineum	3
Breast abscess	2
Bronchopneumonia	2
Cystitis	1
Bartholin's abscess	1
Ether tracheitis	1
Dehydration	1
Influenza	1
Ether pneumonia	1
Upper respiratory infection	1

TABLE V

	DE LEE	BRITISH	STRASSBURG
Dührssen's series	51.4	23.2	14.0
All cases, Oct. 1, 1932, to Oct. 1, 1933	34.5	14.0	6.8
Delivery subsequent to Dührssen's incisions	26.0	10.7	4.5

Maternal Mortality.—Seven women, or 1.18 per cent, were lost in these cases of Dührssen's incisions. There were two anesthetic deaths from ether, one of these being from aspiration pneumonia. One patient died of hemorrhage from abruptio placentae. The patient who survived delivery more than six hours died of subacute bacterial endocarditis with decompensation. Autopsy revealed typical cardiac findings and numerous recent and old infarctions of the spleen and kidney. One patient died in either eclamptic or nephritic coma.

The two remaining patients died from "obstetric shock." One patient lost an estimated 600 c.c. while the other lost only 350 c.c. of blood. In this latter case of sudden death on the table, a diagnosis of thymus death was made. In these two cases the operation must surely be looked upon with suspicion as a strong contributing factor to the shock, if not the sole cause, although both patients received rather long ether anesthesia, one being two hours in duration. The former of these two was returned to her room in good condition with a pulse of 85 and did not appear unduly anemic. She went into shock and died in one hour in spite of stimulants and fluids. No autopsy was granted, but examination of the genital tract revealed no uterine rupture.

All but one of the fatal cases occurred in the first half of the series and neither intravenous fluids nor blood transfusions were used, although several had no appreciable hemorrhage. All the patients who died had ether anesthesia after prolonged labor. In the last 260 cases only one death was encountered. That was of a patient in deep coma when delivery was almost comparable to a posthumous cesarean section. The last 167 consecutive cases up to Jan. 1, 1934, have been free from maternal mortality.

Protocols of Maternal Deaths.—CASE 1.—(No. 8250) Patient, Aug. 7, 1919, aged twenty-one, gravida i, para 0, four weeks overterm, cervix effaced, 8 cm. dilated, meconium in fluid. Delivery was by Dührssen's incisions and easy low forceps. Took anesthesia poorly, became cyanotic, physical findings of aspiration, dead of pulmonary edema two hours and thirty-five minutes after delivery.

Diagnosis: Aspiration pneumonia. Anesthetic death. Autopsy denied.

CASE 2.—(No. 6087) Patient, Feb. 6, 1918, aged thirty-seven, gravida ii, para i, 5 cm. dilated after fifty-five hours labor. The patient went into shock during midforceps operation after Dührssen's incisions and died in thirty minutes. There was no hemorrhage or rupture of the uterus.

Diagnosis: Anesthetic death, no autopsy.

CASE 3.—(No. 12073) Patient, May 16, 1920, aged eighteen, gravida i, para 0. The patient suddenly went into shock near the end of a midforceps operation and promptly died. Ether anesthesia two hours. Estimated blood loss 350 c.c. Autopsy revealed: (1) Enlarged thymus, mesenteric lymph glands, and Peyers patches; (2) pulmonary edema; and (3) bladder and uterus intact. No blood in peritoneal cavity.

Diagnosis: Thymic death ? or obstetric shock.

CASE 4.—(No. 16802) Patient, aged thirty-five, gravida ii, para 0. Multiple pregnancy. In labor thirty-five hours, dehydrated, febrile, one chill. Typical signs of abruptio placentae appeared, delivered by forceps for the first and version and extraction for the second twin. Profuse postpartum hemorrhage, estimated 1400 c.c.

Diagnosis: Abruptio placentae with intra- and postpartum hemorrhage.

CASE 5.—(No. 25459) Patient, Oct. 27, 1922, aged thirty-six, gravida i, para 0. Rheumatic endocarditis since age eleven, with subacute bacterial endocarditis with decompensation in pregnancy. Spontaneous onset of labor at twenty-eight weeks. Ran typical course for the disease and died of cardiac failure on the thirty-eighth day postpartum. Autopsy showed normal genitalia, typical vegetation of mitral and aortic valves, and infarctions of the spleen and kidneys.

Diagnosis: Subacute bacterial endocarditis.

CASE 6.—(No. 25973) Patient, aged twenty-nine, gravida ii, para i. Moderate toxemia. Delivery by high forceps after Dührssen's incisions. Postpartum hemorrhage of 600 c.c. controlled. The patient left the delivery room in good condition with a pulse of 85 and of good quality. She went into shock soon after reaching her room and died in one hour in spite of treatment. No autopsy was granted but exploration of the uterus showed it empty and clean with no rupture.

Diagnosis: Toxemia of pregnancy, vasomotor collapse, obstetric shock.

CASE 7.—(No. 44374) Patient, Aug. 1, 1925, aged thirty-nine, gravida i, para 0, entered the hospital with a blood pressure of 218/128. The urine gave a reaction of 4+ albumin and contained many hyaline and granular casts and red and white blood cells. The patient very soon passed into deep coma and was delivered by Dührssen's incisions and midforceps of a viable baby that survived, but she did not respond to therapy and died in seven and one-half hours. Autopsy was denied.

Diagnosis: Eclamptic or nephritic coma.

Fetal Mortality.—Sixty-one babies were lost either by stillbirth or as neonatal deaths in the hospital giving a percentage of 10.3, which compares favorably with the figure of Shir (13 per cent). Correction for monstrosity, babies under 1,500 gm., and macerated fetus (18 cases), gives a mortality of 7.7 per cent.

It is impossible to give an accurate statement of fact as to the number of babies saved. In approximately 150 patients evidence of fetal distress was deemed

serious enough to be the sole indication for the operative delivery, and in many more there was a combined maternal and fetal indication. Many babies were probably dying or died during the operative extraction, especially by high forceps (Table VI).

TABLE VI. TYPE OF DELIVERY CORRELATED WITH FETAL DEATH

DELIVERY	FETAL DEATHS	NO. DELIVERIES	PER CENT
High forceps	18	86	20.5
Breech extraction	4	32	12.2
Version and extraction	7	66	10.6
Midforceps	17	310	5.5
Low forceps	1	92	1.1

High forceps in this connection means that the fetal head was above the ischial spines as the forceps were applied. It is not synonymous with floating forceps. Only three or four cases of true floating forceps occurred.

The statistics for prolapsed cord (not including "occult" prolapse) are better than the average, namely, 8 deaths out of 18 cases. A mortality of 44.4 per cent which is corrected to 33.3 per cent by deducting 1 monstrosity and 1 previable infant.

Subsequent Labors.—A curiosity regarding the behavior of the incised cervix in subsequent labors was of paramount interest and, in fact, stimulated the present study. Nothing was found in the literature regarding this point. Perhaps because of the transient population of Chicago and the advanced age of many of the patients, a history of only 158 subsequent labors was obtained from a review of the hospital files.

Nineteen deliveries were by cesarean section, chiefly due to previous pelvic dystocia with fetal death. Serious cervical dystocia from dense scarring by previous Dührssen's incisions gave trouble in only six instances. This obstacle was overcome three times by cesarean section, twice by repeated Dührssen's incisions and once by manual dilatation of the cervix with a favorable outcome to mother and baby in each instance.

Labor was quite short, averaging 9.9 hours. Seventy-three patients delivered spontaneously, low or outlet forceps occurred 30 times; 15 patients were delivered by midforceps, 6 by version and extraction, and 4 by breech extraction.

The interval between pregnancies (Table VII) studied in 149 cases showed no predisposition to relative sterility because of Dührssen's incisions. In all patients who could be traced in the records, there were only 6 cases of abortion under thirty-five weeks and 5 premature births over thirty-five weeks. Record of 1 ectopic pregnancy was encountered. Six of the 158 cases had had a trachelorrhaphy between pregnancies, and 7 cervices had been subjected to secondary repair at later deliveries.

TABLE VII. YEARS' INTERVAL BETWEEN PREGNANCIES WITH DELIVERY BY DÜHRSSEN'S INCISIONS AND NEXT SUBSEQUENT PREGNANCY

Under one	1
One year	45
Two years	45
Three	33
Four	22
Five	5
Six	2
Seven	0
Eight	1

One woman died as the result of a complete abruptio placentae (0.62 per cent maternal mortality). Eight babies were lost (5 per cent) but when corrected for monstrosity, previability (under 1,500 gm.), and macerated fetuses, there remains only the 1 fetal death from the severe abruptio placentae which also cost the mother's life.

The blood loss and morbidity were both gratifyingly low. The average estimated blood loss for 145 patients was 246 c.c. Table VI shows the distinctly afebrile morbidity, definitely lower than the average for the entire series.

Subsequent Condition of the Cervix.—Table VIII presents important data relevant to local outcome of the operation on the cervix. Nearly one-half of the patients left much to be desired from the surgical repair of the cervix. It was surprising to notice how many patients presented adhesions to the vaginal fornix from deep cervical scars.

One must not expect too much from the cervix in these cases. It is usually traumatized and often edematous or infected before the operation is begun. A multiparous cervix entirely devoid of all lacerations is a rarity. A good functional result, not anatomic perfection, is all that should be expected.[21]

Unfortunately, the occurrence of troublesome leucorrhea was not studied in specific detail. It did occur, but not with great frequency. In the unsatisfactory cases with poor healing, much good can be done in the way of clearing up a bad cervix

TABLE VIII

CERVICAL RESULTS	NUMBER OF CASES	PER CENT
Well healed	95	54.5
Poorly or not healed	18	10.4
Deep scars	33	19.1
Adhesions to fornix from deep scars	27	15.6
	173	
Repeated Labors		
Well healed	17	37.7
Deep scars	21	64.7
Required repair	7	15.5
	45	

by careful use of the actual cautery or silver nitrate. These cases should be followed until healing is complete. Such is our present practice and results are proving it well worth the time and effort.

The value of the baby in the specific case must be weighed carefully against the possible subsequent danger the mother or fetus may suffer from the operative delivery, and also the chance for the fetus if left to a spontaneous delivery or low forceps after complete dilatation and descent of the fetal head. The ultimate social value of some of these infants subjected to premature operative delivery may, we feel, be questioned because of trauma inflicted, even though in no patient did this appear evident on discharge from the hospital.

SUMMARY AND CONCLUSIONS

1. Dührssen's incisions offer a rapid surgical method to complete the dilatation of the cervix when urgent need for delivery arises, and when the cervix is the only obstructing factor.

2. Careful placing and timing of the indication in the individual case is required. Careful supportive therapy directed to forestall or treat the deleterious effects of exhaustion and dehydration will lessen the

necessity for the radical procedure. Because of better treatment in the first stage and because of the relatively greater safety of cesarean section, the incidence of Dührssen's incisions should fall but the procedure will remain valuable in a limited field. When the dye has almost irrevocably been cast in favor of delivery from below in long and potentially infected cases, its usefulness is obvious.

3. A series of 592 cases is analyzed. These cases were among the most troublesome of the 40,000 in which they occurred because of the high incidence of, (a) mechanical induction (1 out of 5), (b) overterm pregnancies with large babies, (c) elderly primiparas, (d) occipitoposterior and transverse positions (84 per cent), (e) long labors with poor uterine action, (f) early rupture of the membranes, (g) high incidence of borderline contraction of the pelvis, and (h) difficult endocrine types.

4. Placenta previa is a contraindication for Dührssen's incisions. A second contraindication is dystocia due to: (1) malposition of the fetus, (2) large fetal head, (3) a small pelvis. The procedure is surely not one to be contemplated at the onset of labor as a method of delivery but rather it is often the best available means of meeting an untoward or undesirable exigency. It should not compete with cesarean section in cases of pelvic dystocia.

5. Some patients should have been subjected to cesarean section after a failure in a shorter test of labor.

6. Procrastination, after failure of progress of from six to ten hours with good pains following a protracted labor with the membranes long ruptured and without contraindication, courts increased maternal danger especially from morbidity.

7. The operation is not without some small but real danger to the mother of death from shock and hemorrhage. Dührssen's incisions were directly responsible in only one or two cases for the maternal mortality. Fatal cases were in the earlier portion of the series; all received ether anesthesia and none the benefit of any kind of intravenous therapy.

8. A high morbidity must be expected from the nature of these cases. There were no deaths from puerperal sepsis in the entire series (624 cases until Jan. 1, 1934).

9. Three incisions made to the fornix if necessary are recommended to avoid serious extension.

10. Edema of the cervix is more prone to cause hemorrhage than the nonedematous thick cervix, but more safety is assured with a thin cervix affording good retraction of the uterine vessels and their branches. Effacement, i.e., dilatation of the internal os and retraction of the lower uterine segment, is imperative, before the incisions are made.

11. While the fetal mortality is high (10.3 per cent) some evidence points toward the possible conservation of fetal life. Both fetal and maternal risks are tremendously diminished if a low forceps can be done rather than mid or high forceps.

12. The end-results of cervical healing are excellent in slightly over one-half of the cases, but somewhat disappointing in the remainder. Careful follow-up therapy with the cautery or silver nitrate will usually leave a clean cervix.

13. Except for a small minority of about 4 per cent, which must not be overlooked, the labors of subsequent pregnancies are quite uneventful as regards cervical dystocia. In fact, they seem to deliver with greater ease and safety than the average obstetric patient, providing cervical obstruction was the cause of the dystocia in the first labor.

14. Dührssen's incisions leave no increased tendency toward abortion, miscarriage, ectopic pregnancy, or reduced fertility.

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Tietze, K.: Follicle Persistence and Glandular Hyperplasia of the Endometrium, Arch. f. Gynäk. 155: 525, 1934.

Tietze reports his studies of 466 patients seen during the last ten years in the Kiel clinic. In all of these patients there was follicle persistence and glandular hyperplasia of the endometrium, a condition usually described as metropathia hemorrhagica. The author points out the comparative frequency with which these conditions are found at the beginning and the end of the period of sex activity, i.e., at puberty and at the menopause.

In the differential diagnosis of this condition, all other types of acyclic vaginal hemorrhage must be ruled out, namely incomplete abortion, endometritis, polyps, submucous fibroids, and carcinoma of both the cervix and the fundus. Various forms of hyperplasia following pregnancy and the various types of hemorrhages found in connection with this condition are discussed. Anatomic studies of the endometrium, myometrium and of the ovaries are described and the author states that large cystic granulosa-bearing follicles were found in all but one patient. As a result of this, hyperplasia of the endometrium, the myometrium and the endosalpinx was almost universal. The hyperplastic endometrium was undoubtedly the source of the hemorrhages.

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ARGYRIA UTERI

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THE fact that argyria has not yet been mentioned in gynecologic literature induces me to report the following case of chronic silver poisoning.

A woman of fifty-seven years was referred to me by Dr. O. H. Wilhelmi for treatment of uterine prolapse. She had given birth to two children and was now two years past the menopause. For two years she had been troubled with dysuria, bearing down, and difficulties in locomotion and, on gynecologic examination, presented a very large cystocele, an incomplete prolapse of the uterus and a large polyp springing from the posterior lip of the cervix.

More interesting and pertinent to the subject of this paper were her general appearance and the history of her former health. About five years previously she had been treated for a gastric ulcer with pills containing ¼ gr. of silver nitrate which she took three times daily for fifteen months. She discontinued this medication only when she found no relief from her digestive distress. Subsequently she changed her medical attendant and eventually recovered completely.

Although she claimed that she now looked "50 per cent better" than five years age, she still presented a typical picture of pronounced argyria. The skin of her face, neck, and hands was of a dark slaty color. The surface of the body which had not been exposed to direct sunlight was less deeply pigmented, yet definitely grayish in appearance. The tip of her nose and the lips appeared cyanotic; the cartilaginous parts of the external auditory canal, bluish gray; the tympanum, dark. The sclerae were slightly icteric; the conjunctivae and buccal mucosa, bluish. The gums alone were normal in color; all her teeth had been extracted years before she took the silver nitrate pills. The finger nails had that deep gray discoloration that one may see in the dead. The protruding vaginal walls were more grayish than blue.

The genital affection clearly called for surgical intervention, but her general appearance was somewhat intimidating. A search in the literature for specific guidance was unsuccessful. A very thorough general examination, however, revealed perfectly normal conditions of heart, lungs, and kidneys. Blood pressure, clotting time, nonprotein nitrogen, and blood count were likewise entirely normal. Under these circumstances I felt justified in performing the operation. The latter consisted of a vaginal hysterectomy with the technic described elsewhere,[3] and a perineorrhaphy, both under local anesthesia, and both procedures were carried out painlessly and bloodlessly. Her recovery was undisturbed. All wounds healed by primary union; the patient left the hospital in fourteen days, and resumed her household duties four weeks later.

Of special interest was, of course, the condition of the uterus. This organ was immediately after removal wrapped in a towel so as to eliminate any possible effect of daylight, and taken to the laboratory. The outside seemed unchanged as to

color, but on bisection the ordinarily white walls appeared a light tan. After being placed in a specimen jar, the tan gradually became darker and the formalin solution assumed the same color.

Unstained frozen sections made from the fresh specimen showed here and there some brownish opaque material in small clumps, but its relation to the surrounding tissues could not be determined. In paraffin sections stained with hematoxylin-eosin, silver deposits were not discernible, but they became visible when the sections were stained only lightly with alum carmine and examined under high power. Very fine black dots were seen chiefly in the musculature of medium and large-sized vessels and also throughout the musculature of the uterus. In the multiple squamous epithelium of the cervix they were entirely absent; neither could they be found in the subepithelial tissues, and only very occasionally was a black dot discovered in one of the papillae. A few lumina of the cervical and uterine glands were seen surrounded by a fine black line, but as a whole the endometrium was free. The oil immersion lens, finally, showed these black particles to be either very small, fairly

Fig. 1.—Argyria uteri. Section through uterine muscle, very faintly stained with alum carmine. The entire field appears darkened, owing to the wide distribution of extremely fine, dustlike black particles throughout the tissues (best seen with oil immersion). Connective tissue and elastic fibers appear as wavy black lines upon which fine granules can be seen arranged in rows here and there. In the walls of arteries and veins larger granules are visible. Note, in particular, the presence of such granules within the contents of the veins in the left lower and right upper corner.

even-sized granules or extremely minute dustlike deposits scattered diffusely throughout the myometrium. Nowhere were any signs whatever of a foreign body reaction in the form of leucocytes, lymphocytes or giant cells.

These findings were presented and the patient was demonstrated before a local medical society, but the publication of the case was delayed for extraneous reasons. Now that the uterus has been in the hardening solution for more than a year, the specimen has turned a very dark, almost black color. New sections made present a much clearer picture which is represented in Fig. 1. The deposits are now much more numerous and better defined. Connective tissue and elastic fibers appear black, and with the oil immersion finest granules can be seen upon them like beads on a string. A fine black line separates the endothelium in many of the arteries from the media; within the latter and at their periphery there are other granules. In the veins larger granules are easily seen at the periphery and *also among the blood*

cells which fill their lumina. This interesting phenomenon is *not* an artefact. A dense shower of minutest black dustlike particles extend diffusely throughout the musculature. The superficial epithelium of cervix and endometrium are even now quite free, and in the uterine mucosa the distribution of silver deposits corresponds to that observed in the earlier sections.

DISCUSSION

Argyria is nowadays much less common than it was in former years. Its etiology is twofold: occupational and medicinal. There used to be many cases of chronic silver poisoning among silver miners, silversmiths, silver leaf workers, and those engaged in the industry of silvering glass pearls,[5, 8, 16] but modern methods of hygiene have largely removed this vocational hazard.

The medicinal factor manifested itself at the time when silver nitrate, given by mouth, was commonly used in the treatment of epilepsy, chorea, tabes, and, later, of gastric ulcer.[4, 7, 12] The recognition of the inefficacy of this therapy and its subsequent abandonment checked the further production of argyria. More recently, however, protracted use of overdoses of colloidal silver preparations such as argyrol, protargol, collargol, and neosilvol, principally for catarrhal conditions of the respiratory passages or for the prevention of such conditions, has brought forth a new crop of cases of argyria, this time chiefly in children.[10, 11, 14, 17] Even long-continued topical applications of solutions in chronic conjunctivitis or lid eczema are known to have been followed by argyrosis.

The chemical industry is constantly putting new preparations of this sort on the market with trade names which do not suggest their silver content. A case in point is the German *adsorgan* to which already several instances of chronic silver poisoning have been traced.[7, 13] That an overdose of silver-arsphenamine may be productive of argyria has been shown by Becker and Ritchie[1] on two cases, and the same may be true of intravenous collargol injections which enjoyed a brief popularity in puerperal sepsis.

The silver which enters the organism in excessive amounts, whether swallowed or absorbed from the visible mucous membranes, permeates the entire body and is deposited in *all* organs and tissues where it becomes permanently fixed in the form of very small and nearly even-sized black or grayish granules.[4, 12] The resulting pigmentation is most striking in the skin, lymph nodes, glomeruli, and choroid plexus of the ventricles. No part of the body is exempt though the brain substance itself seems least affected. The outer appearance of patients with pronounced argyria is, indeed, startling and unforgettable to any one who has seen them; they almost resemble corpses that have suddenly come to life. My patient unquestionably was of this category. In her case, too, the discoloration of all visible mucous membranes, the external auditory canal, and the tympanum corresponded to the de-

scription of former observers. She also had icteric sclerae and darkened conjunctivae; further ophthalmologic examinations were not made but I infer from the literature that the internal parts of the eyes may likewise be affected. The gums, as a rule, remain free while the teeth may exhibit a dark greenish brown tint. The nails, as in my patient, are of that dark gray color which usually appears after death, and there are cases on record where the hair of the head had assumed a yellowish red hue,[6] and added a still more phantasmal touch to the startling picture. As regards inner organs, Petri[12] supplies several colored illustrations which demonstrate the dark appearance of the intestinal mucosa; and it will be remembered that in my case, the uterine musculature exhibited a distinct yellowish brown discoloration.

Our knowledge of the finer histologic processes in chronic silver poisoning which dates back to the publication by Frommann,[2] in 1859, has been obtained from biopsies and from postmortem examinations of which I have been able to find only 13 instances in the literature.[2, 4] In all of these 13, conditions other than chronic silver poisoning were the causes of death. In these examinations, all organs have been subjected to careful study, but as all previous reports dealt with male patients, this, as far as I could ascertain, is the first time that the uterus has become available for study.

All observers agree that the silver deposits produce no reaction whatever in the tissues, and my case bears out this contention. The silver granules seem to have a particular predilection for connective tissue and even more markedly for elastic fibers. Whether this is due to some sort of chemical affinity or whether these fibers act as filters, has not yet been determined. At any rate it is along the bundles of collagenous and elastic fibers, but not *within* epithelial cells that the granules group themselves in the form of rows.[4] Petri[12] notes in particular that in the heart muscle the granules cover the sarcolemma as a dense sheet. The distribution of these deposits is most dense where the blood supply is particularly abundant as seen, for instance, in the glomeruli of the kidney. My findings of granules *within* the venous blood stream well illustrate this point. In contradistinction to other writers,[4, 14] who described rows of granules in the connective tissue underlying secreting epithelium, I found but few such deposits in the neighborhood of glands. Once deposited in tissues, the silver becomes permanently fixed, and apparently no part of it is excreted. It has been suggested that the silver nitrate is first changed into silver albuminate, then dissolved, and finally reduced to metallic silver.

After this paper was written, Dworzak (Zentralbl. f. Gynäk. 58: 169, 1934) published his observations on a case of local argyrosis of a cervical polyp. In this case a small erosion had repeatedly been touched with a 20 per cent silver nitrate solution. One year later a small polyp of dark color was found protruding from the external os. Microscopically, the surface of the polyp was covered with a wide,

dark brown layer of pigment and the intracellular substance of the epithelium was deeply impregnated with pigmented granules and gave the multiple squamous epithelium the appearance of a network. Dworzak used silver nitrate solution experimentally on a number of cases of erosion and polyp and found that impregnation always took place after two days. Though in his cases the effect of the topical application of silver nitrate remained localized upon the surface, the report is here interposed for the sake of completeness.

The amount of silver intake sufficient to produce argyria, and the time of its first outward manifestations range between wide limits. The case reported by Koelsch[9] where 2 gm. were taken within two months, thus far represents the minimum record. In the necropsy conducted by Goettler and others,[4] the silver content of the entire body was estimated as between 90 and 100 gm. My patient took at least 150 gm. during a period of fifteen months, but the first signs of argyria appeared about nine months after starting the treatment. In Lundy's case[10] between 200 and 300 gm. of neosilvol were used as nose drops for three and one-half years before any marked discoloration was noticed; and in the case reported by Knack[7] argyria did not become manifest until five years after the first medication.

It is obviously due to the utter lack of tissue response which is quite unlike the cellular reaction to other foreign bodies, that the general health is not affected in argyria. This is uniformly stated in all published reports; and in the description of my own case I have emphasized that all bodily functions and findings were unimpaired. It is precisely for this reason that Petri[12] questions whether we are quite justified in classifying argyria among the chronic poisonings.

Therapeutically the condition is unchangeable. Stillians and Lawless[15] produced localized areas of argyria by injecting a mild silver protein solution into their own arms. They succeeded in removing the bluish discoloration by injecting into the affected spots a solution containing 0.25 per cent potassium ferricyanide and 6 per cent sodium thiosulphate, thus imitating a photographic reduction process which gives equally good results with fresh or old negatives. Interesting as this experiment is, it has, of course, no practical applicability in our problem.

SUMMARY

Argyria or chronic silver poisoning, once a fairly common condition, has now become a rare disease for reasons set forth in the body of this paper. Afflicted persons present an appearance of such startling singularity that in a pronounced case the diagnosis is unmistakable. The silver permeates the entire body and is deposited in all organs and tissues in the form of minute granules without producing the usual foreign body reactions. Argyria has not yet been mentioned in the gynecologic literature of the world because all published records deal only with men or children. A fortuitous chance gave the author the opportunity to remove the uterus in a woman with a very pronounced argyria and to add his histologic studies of this organ to the chapter on chronic silver poisoning.

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METROPOLITAN BUILDING

VARYING PATTERNS OF DRIED BLOOD SERUM OF WOMEN

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DU NOUY, and later V. Bergauer, Boučik, and V. Podgrouzěk[1] show that when diluted blood serum, taken from women at different periods in the menstrual cycle, is dried on slides, the salt crystals deposited take different forms. These authors claim that such different patterns are not due to chemical changes. The albumin-globulin content of the serums was tested by Robertson's refraction method. No differences were detected, and the addition of globulin and cholesterin to the serums had no effect on the dried patterns deposited. No changes in the concentration of hydrogen ions could be found.

These authors are of the opinion that the difference in the patterns depends upon the hormone content of the serums. The patterns could be altered by the addition of extracts of thyroid, ovary, or hypophysis. It is the theory of these writers that the hormones in the blood influence the electrolytic condition of the serum, and hence affect the form of the salt crystals deposited on drying.

The authors describe three types of patterns which we illustrate in the accompanying plates photographed from our own specimens. Fig. 1 shows the "bastioned" type, which shows a single sodium chloride crystal surrounded by a ragged rampart of more irregular débris and crystals, looking, under the low power of the microscope, like the ground plan of a fortification. This type of figure is said to be characteristic of serum taken within less than a week after a menstrual period. Fig. 2 presents the single crystal surrounded by concentric rings, of a "cut onion" appearance. This is supposed to be the type

found midway between menses. Fig. 3 shows the concentric rings more broken in their continuity. This picture is assigned to a few

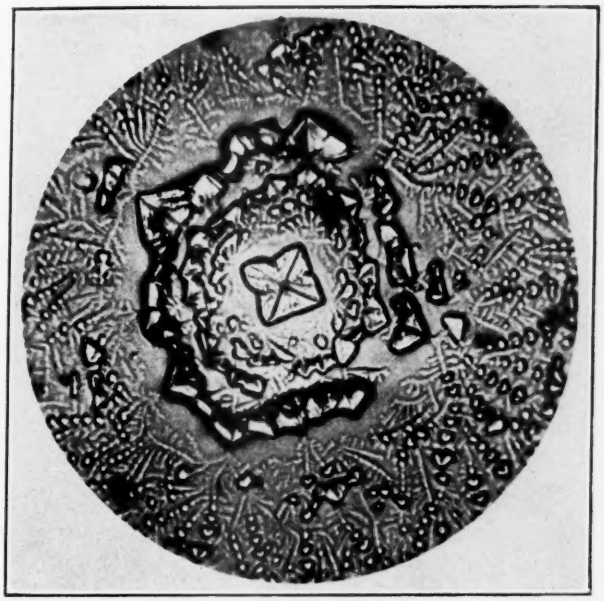

Fig. 1.—"Bastioned." Early postmenstrual.

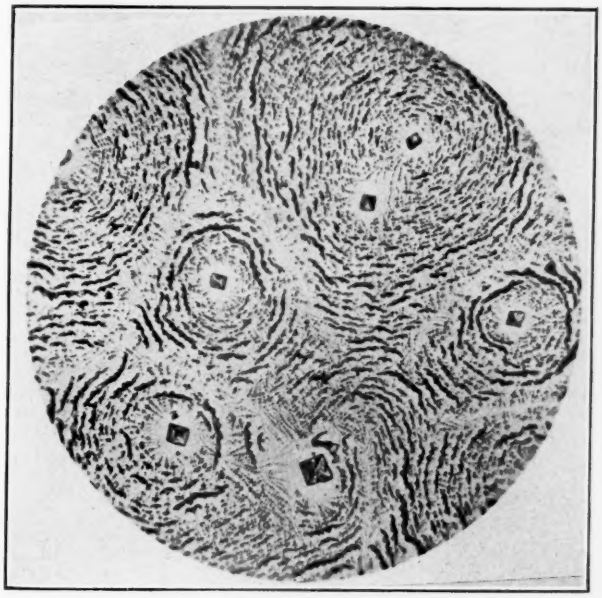

Fig. 2.—Ringed. Intermenstrual.

days premenstrual. We have added two types to these three described by V. Bergauer and others. We found that Fig. 4, distinctly radiant,

is more characteristic of the premenstrual period; and we also observed it frequently in male controls, in pregnancy, and in the post-

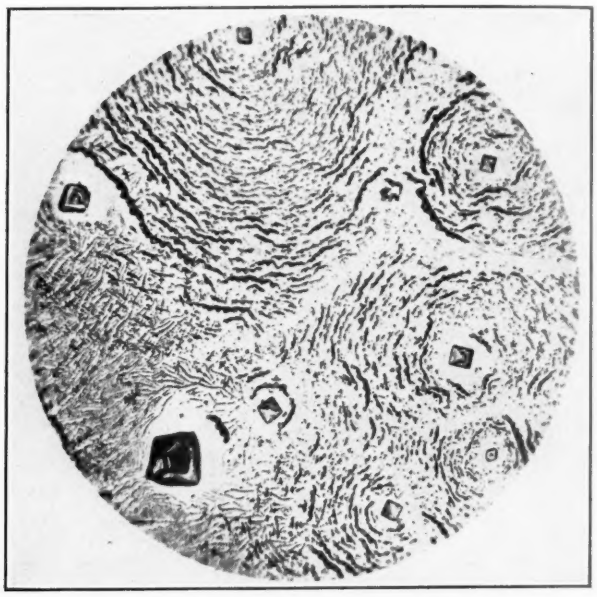

Fig. 3.—Interrupted rings. Premenstrual.

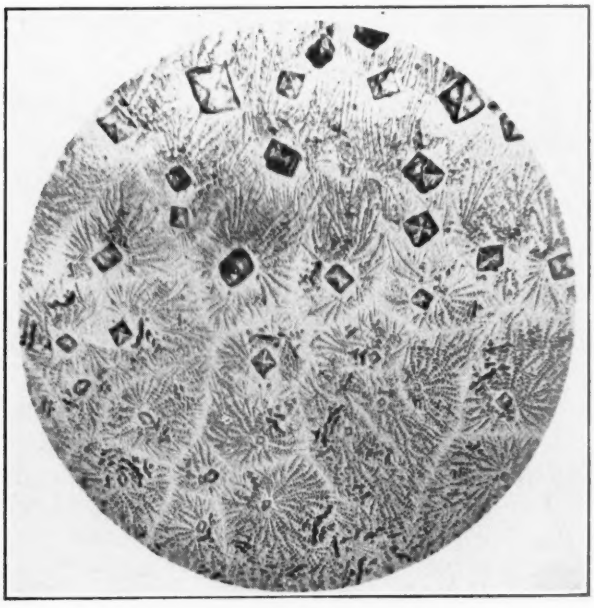

Fig. 4.—Radiant. Premenstrual, male, pregnancy.

partum period. Fig. 5 shows larger asters than does Fig. 4; a condition we have found in toxemias and eclampsia.

V. Bergauer and others describe the simple technic for these observations. They emphasize the importance of uniform drying temperature and of uniform dilution. A dilution of 1 to 10 is satisfactory. We use a standard white blood corpuscle counting pipette, drawing the blood up to the 0.1 c.c. mark and filling the bulb to the 1 c.c. mark with normal saline solution. It is not absolutely necessary to remove the corpuscles, but we do centrifuge the dilution. A drop of the clear fluid is deposited on a slide, which is dried in the incubator at 37° C. for twenty-four hours.

We have other evidence that the hormone content of the blood varies at different periods of the menstrual cycle. For example, Frank and others[2] state, "40 c.c. of blood regularly give a positive reaction

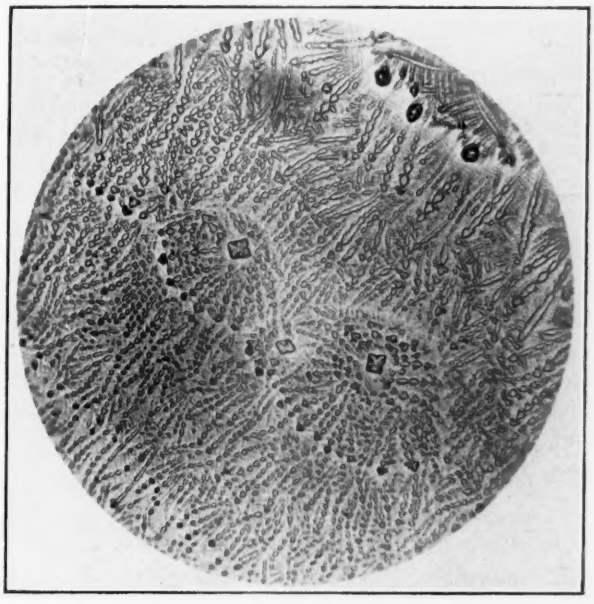

Fig. 5.—Large asters. Toxemias.

(for theelin) some twenty-one days before the onset of the menses; 30 c.c. are positive between the twenty-first, and fourteenth day; 20 to 10 c.c. are positive from the seventh day preceding the period until menstruation." The theory that pregnancy toxemia and eclampsia may be due to increased amounts of circulating hormone, as expressed recently by Hofbauer[3] and others, is supported by Frank's[2] sentence, "By the sixth week of pregnancy, the reaction with 8 to 10 c.c. of blood is regularly positive." Of course, not merely is the gonadotrophic hormone thus increased in pregnancy, but also progestin and many or all of the other hormones.

V. Bergauer and others had worked only with blood from nonpregnant women. If the patterns are altered by changing hormone con-

tent, and if hormones do increase in amount during pregnancy and in toxemia, we thought it would be interesting to test bloods from pregnant women. Through the kindness of Dr. Arthur H. Bill, we have been able to do this with patients from the dispensary and wards of the Cleveland Maternity Hospital. As Table I indicates, the results have not been uniform, but the blood pattern in normal pregnancy seems to fall most frequently into Class IV, while the toxemias and eclamptics tend to Type V, of large asters.

TABLE I

	POSTMENSTRUAL; DAYS				PREGNANCY		TOX.	ECLAMP.	MALE CONTROL
	1-7	7-14	14-21	21-28	1ST HALF	2ND HALF			
Type I "Bastioned"	3								
Type II Ringed	2	6							
Type III Interrupted ring	6	9	6	3	2	2	1		
Type IV Radiant	3	4	9	3	1	8	1		5
Type V Large asters	1					2	5	3	

CONCLUSIONS

1. Dried drops of diluted blood serum from women show the deposited crystals arranged in at least five different patterns.

2. The predominant type in pregnancy and the toxemias is either Type IV or V, and unlike that seen in the case of most nonpregnant women in the early postmenstrual days.

3. The patterns are not consistent enough to be very reliable for diagnostic purposes, but they may aid in evaluating the amounts of circulating hormones.

I wish to express my gratitude to Dr. E. E. Ecker, of the Western Reserve Medical School, for important assistance in this work.

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INTERSTITIAL RADIATION OF THE CERVIX, WITH A SUGGESTED MODIFICATION OF TAUSSIG'S OPERATION*

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THE therapy of carcinoma of the cervix is still in the experimental stage. The results in most clinics are not too gratifying.

The radical hysterectomy of Wertheim, or the radical vaginal hysterectomy of Schauta and Peham are only applicable to the Group I cases, and are attended by a high operative mortality.

The usual roentgen and radium irradiation that is so extensively used, fails so frequently, only giving a short period when the cervical lesion heals, and the patient has a feeling of well-being, gain of some weight, only to be followed in a few months by parametrial or glandular metastases, with continued progress of the growth. The roentgen therapy is continued then with no avail.

The wave length of our 200 kilovolt roentgen machines cannot equal the gamma rays of radium. Hence they are not as effectual in destroying the neoplastic cells as the radium was in primary growth.

When we consider that the gamma rays of radium decrease in direct proportion to the square root of the distance, we can readily see that glandular or parametrial metastases will not be destroyed by these rays.

It is the belief of Taussig[1] and many others that the lymph gland metastases are more radioresistant than the primary growth.

With these facts in view we are searching for a method to control the progress of extension in our cases, and have tried interstitial radiation in a few cases by implanting radon seeds by the abdominal route.

Interstitial radiation with radon seeds was first employed by Janeway in 1915. Since then it has been used by many others, and in recent years by Taussig[1] and Gellhorn.[2]

Delporte and Cahen[3] use interstitial radiation with radium element in needles implanted in the lower uterine segment and capsules implanted between the layers of the broad ligaments. This is done six weeks after their original radiation of the cervix.

Cancer of the cervix spreads by directed extension in the tissues and by glandular metastases. In the direct tissue extensions occurring a few months after initial radiation some cases may be controlled by implanting radon seeds from the vaginal route, but can be reached more effectually by the abdominal route.

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1935.

In regard to the lymph gland metastases Taussig has made a wonderful contribution by his lymphadenectomy and interstitial radiation. He reports over 61 per cent of Group II patients living and well from one to three and a half years. In these patients he found carcinomatous lymph glands in 44.4 per cent. Without this additional operative therapy his percentage of cures would probably have been reduced by one-half.

Since Feb. 1, 1933, to June 1, 1935, we have admitted to Kings County Hospital 131 cases of carcinoma of the cervix. Of these there were 68 or 52 per cent which were so hopeless that no therapy was attempted. There were 29 or 22 per cent of advanced clinical Group IV cases in which palliative therapy was attempted. There were 19 or 14 per cent of clinical Group III cases, 16 or 9 per cent of clinical Group II, and 4 or 3 per cent clinical Group I cases.

Of these we have used abdominal interstitial radiation with radon seeds in nine cases, following our usual local cervical and uterine radiation with radium and an intensive cycle of roentgen therapy.

Radon seed implantation in metastases was done in three cases. Lymphadenectomy with seed implantation in three cases. One patient had abdominal seed implantation, interstitial needle implantation in the cervix, followed a few months later with seed implantation in the cervix, and finally, fifteen months after the original treatment by abdominal hysterectomy and lymphadenectomy, and implantation of seeds in solid metastases against the pelvic wall. This patient was operated upon Sept. 9, 1935, and the outcome of her case cannot be reported. The reason for the hysterectomy was a persistent radioresistant growth on the cervix, and the formation of metastases while receiving intensive roentgen therapy.

The case of our first patient treated by seed implantation in a metastasis will be reported in detail.

Mrs. M. A., aged forty-nine, para iv, was admitted to St. John's Hospital Aug. 31, 1931, with a history of vaginal bleeding for two and a half months. The growth covered the whole cervix and the uterine canal was not patent. Biopsy revealed an epidermoid carcinoma. She was given 4,800 mg. element hours of radiation. This was followed by roentgen therapy at St. Mary's Hospital, where she received a total of 7,310 r. units.

Seventeen months later she was admitted to the Kings County Hospital with the cervix entirely healed and a metastasis in the lower part of the right broad ligament, extending posteriorly. A laparotomy was done with implantation of 13 gold radon seeds of 1.3 mc. each, giving a total radiation dose of 1,490 mc. hours (Fig. 1). This was followed by 5,200 r. unit cycle of roentgen therapy. Eight months later she received 2,130 mg. element hours of radiation in the right vaginal fornix.

In June, 1934, nearly three years after the original treatment, there was a question as to whether the parametrial extension had been cured, and a second laparotomy was done. On opening the abdomen there was no carcinoma found; the mass which had been felt was due to adhesions and fibrosis, and a small retroverted dextra flexed uterus. There were innumerable yellow millet seed sized growths spread

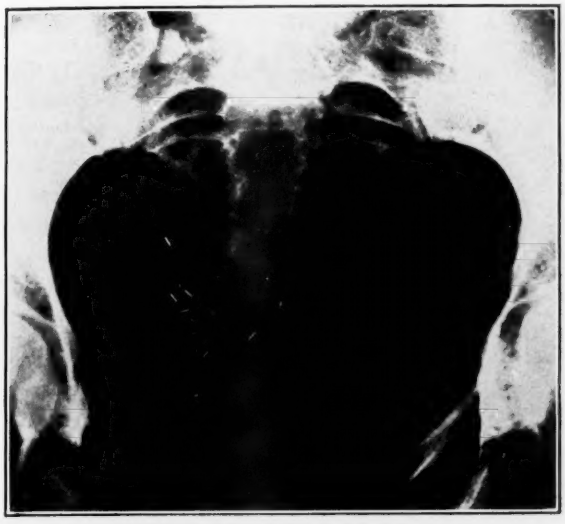

Fig. 1.—Roentgenogram of gold radon seeds implanted in the parametrial metastasis of the case reported.

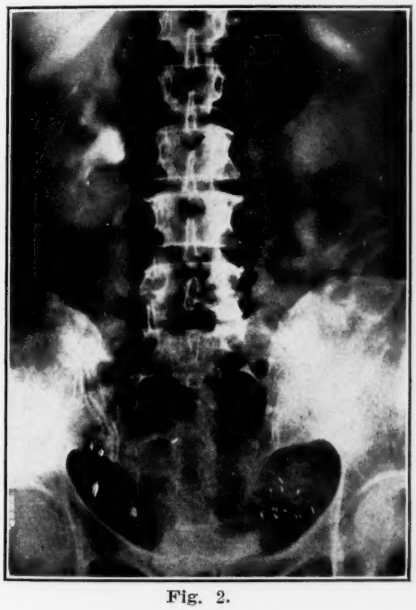

Fig. 2.

Fig. 3.

Fig. 2.—Roentgenogram of intravenous urography taken six months after implantation of gold radon seeds in a left parametrial metastasis. Shows absence of the left kidney or complete loss of function which occurs very early after complete obstruction of the ureter. The left ureteral opening could not be found on cystoscopy. The urography should have been done prior to radiation.

Fig. 3.—Roentgenogram of intravenous urography taken four months after interstitial radiation with gold radon seeds. Shows obstruction of the lower left ureter with dilatation of the ureter and kidney pelvis with beginning loss of function due to a metastasis to the base of the bladder. The function of the right kidney is still good.

over the peritoneum, intestines, uterus, tubes, and broad ligaments. One of these situated in the left tube was excised for pathologic study. The report showed it to be composed of fibrotic connective tissue, with involuntary muscle fibers with which are quite a number of blood vessels, some of which the lumen completely obliterated. No evidence of malignancy was present; probably result of previous radiation therapy.

This patient has had no further treatment, and is now past four years from the original treatment, and is in perfect health.

A thorough urologic examination should precede radiation for cervical cancer, and is essential before interstitial radiation. It should consist of a cystoscopy for bladder metastases, or extrinsic tumor pressure, with the passage of large ureteral catheters, or better still, No. 8 Braasch bulbs, to disclose the presence of congenital or old inflamma-

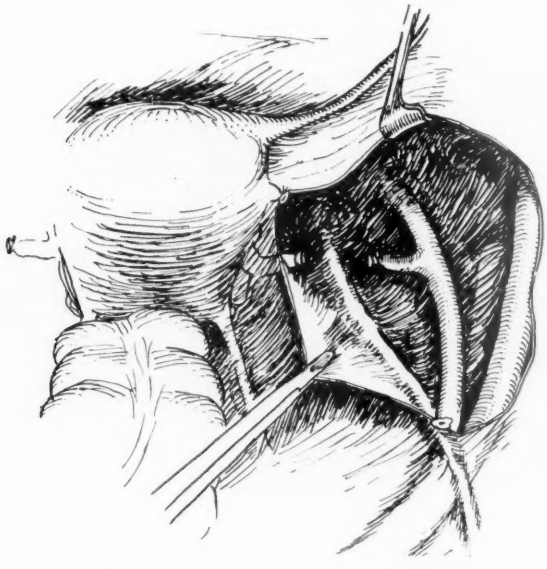

Fig. 4.—The right ovary and tube have been removed. The layers of the broad ligament have been separated. The ureter is shown attached to the posterior layer. The uterine artery has been resected where it crosses the ureter. This reduces the blood supply to the primary growth.

tory strictures of the ureters or occlusion by extrinsic growths. If ureteral obstruction or reduced kidney function is found, an intravenous urographic study is indicated (Figs. 2 and 3).

A cystoscopy with introduction of large ureteral catheters should be done at the time of operation to show the course of the ureters and make identification easy. Radon seeds should not be placed nearer than 1 cm. to the ureters as fibrosis and constriction might occur.

Cystoscopy and examination of the ureters should be repeated two months after radiation, and, if constriction has occurred, repeated dilatation should be done. Large blood vessels must be carefully avoided. If seeds are implanted in too close proximity to the veins thrombi may occur, followed by pulmonary embolus.

SUGGESTED MODIFICATION OF TAUSSIG'S OPERATION

Taussig's technic consists of a bilateral salpingo-oophorectomy with lymphadenectomy of the primary lymph glands, the iliac, obturator, and ureteral, with implantation of radon seeds at the bifurcation of the iliac vessels and in the sacrouterine ligaments. This is done as an initial procedure and radium is inserted into the uterus and cervix at the same time.

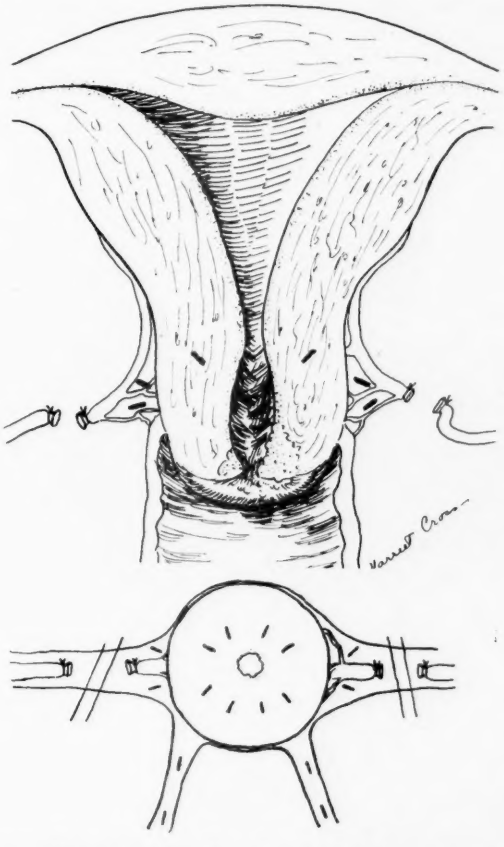

Fig. 5.—The upper diagram shows the uterus with the uterine arteries resected. Radon seeds implanted in the parametria and lower uterine segment. The lower diagram is a cross-section of the uterus showing the clockwise arrangement of 8 radon seeds implanted in the lower uterine segment and 2 seeds in each broad ligament close to the uterus, enough distance from the ureters not to cause marked fibrosis and contraction. Two seeds are implanted in each sacrouterine ligament.

I wish to suggest the following modification to his procedure:

1. That the patient receive the initial roentgen and radium irradiation locally two months prior to operation. That the radium dose not exceed 6,000 mg. hours.

2. That the blood supply of the uterus be reduced by the resection of the uterine arteries (Fig. 4), as reduction of blood supply decreases the spread of malignant tumors.

3. That sixteen 1 mc. radon seeds be implanted; eight in the lower uterine segment, two in each broad ligament near the uterus, and two in each sacrouterine ligament (Fig. 5). This would give a total radiation dose of 2,128 mc. hours.

4. That all the retroperitoneal fat that is exposed be removed, for it may contain small lymph nodes.

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DOUBLE MALIGNANT TUMORS OF THE UTERUS*

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Two malignant tumors in the same uterus constitute an extremely rare and unexpected finding. While the symptoms are the same as those usually found in malignant disease of the uterus, the interest that this condition aroused prompted us to report two cases which were seen at the same time on the surgical service of one of us (Counseller).

REVIEW OF THE LITERATURE

Multiple primary malignant growths have been reported many times. The first case was reported by Billroth, in 1869. The patient in this case was a man who was suffering from carcinoma of the stomach and an epithelioma of the external ear. Since then, Warren and Gates have reviewed all of the cases that have been reported. At the time of the writing of their article in 1932 these had reached 1,259. The great majority of the reports in this large series concerned two different primary malignant tumors, but strikingly enough, in 111 cases there were three or more primary malignant tumors. Rappin reported a case in which the patient was a woman, aged fifty years, who had 251 different epitheliomas of the basal cell type.

The frequency with which multiple primary malignant tumors occur is of interest, although difficult to determine exactly as reports vary according to their source. In Germany, Junghans found that the incidence was only 0.5 per cent in 4,192 cases in which patients who had malignant disease came to necropsy, and Brandt and Jekabson reported the same incidence (0.5 per cent) in 2,083 similar cases. Hanlon of the Mayo Clinic found that the incidence was 2.5 per cent in 710 similar cases. The incidence in the 1,078 cases reviewed by Warren and Gates was 3.7 per cent. Schreiner and Wehr studied the microscopic sections of tissue removed in 11,212 cases of malignant disease and found the malignant tumors to be multiple in 2.7 per cent of the cases. Hurt and Broders in a similar report found the incidence to be 3.3 per cent in 2,124 cases of malignant disease seen at the Mayo Clinic. The

*Submitted for publication October 5, 1935.

highest incidence is reported by Ward who found that in 5.2 per cent of 1,773 cases of epithelioma of the skin, the tumors were multiple. However, his investigation was confined to epithelioma of the skin.

A comparison of the incidence of multiple malignant tumors of the same organ, and of different organs of the same patient, reveals that the former are much more rare. According to Warren and Gates, the skin is the organ which is most frequently the site of multiple primary malignant tumors. The large intestine, pharynx, and stomach, in the order named, are the next most frequent sites. Thus, it may be seen that multiple primary malignant tumors of the uterus are unusually rare. Eighteen cases have been reported previously. Twelve were collected by Warren and Gates. Of these, seven were reported as adenocarcinoma and squamous cell carcinoma, and the remaining five were designated as adenocarcinoma and carcinoma, or as double carcinoma. Major found five other cases of multiple malignant tumors of the uterus. In four of these cases adenocarcinoma was associated with sarcoma, and in the other case adenocarcinoma was associated with a squamous cell epithelioma. Hurt and Broders found a uterus which contained an adenocarcinoma, Grade 4, of the fundus and polyp which disclosed an adenocarcinoma, Grade 1.

REPORT OF CASES

CASE 1.—A married woman, aged forty-four years, came to the clinic because of excessive bleeding from the vagina. Her mother had died of carcinoma of the uterus and a sister had died of carcinoma, which the present patient thought had involved the uterus. The patient previously had been in good health and the menstrual cycle had been normal. She never had been pregnant.

Six months before she came to the clinic, her menstrual period had not ceased, but a small amount of flow had continued and two to three pads had been required each day. At times, the amount of flow had increased and had been associated with dull pain in the lower part of the abdomen. Three months before she registered at the clinic, she had noted a yellowish vaginal discharge that had been mixed with the blood. Her physician had performed a dilatation and curettage. A diagnosis of carcinoma of the fundus uteri had been made, and 50 mg. of radium was inserted for forty-eight hours. Two weeks later roentgenotherapy had been employed. A month later the bleeding had stopped but the yellowish discharge had continued. She had lost 5 pounds (2.3 kg.) since the onset of her symptoms.

Physical examination at the clinic revealed a pale, obese woman who weighed 173 pounds (78.5 kg.). There was slight tenderness in the lower part of the abdomen. The cervix was eroded and bled easily, but did not suggest a definite malignant appearance. The uterus was about two times normal size, irregular, and fixed posteriorly. Examinations of the blood and urine did not reveal anything abnormal. A roentgenogram of the thorax was normal.

Operation was advised and a total abdominal hysterectomy with bilateral salpingo-oophorectomy was carried out. Two weeks later, after an uneventful convalescence, deep roentgenotherapy was applied to four areas on the anterior, posterior, and lateral aspects of the pelvis, on four consecutive days.

A mixed squamous-cell epithelioma, Grade 3, and an adenocarcinoma which measured 4 by 4 by 1 cm. were found at the internal os of the uterus (Figs. 1, 2, and 3). In addition, there was an adenocarcinoma, Grade 1, lying for the most part in the left uterine horn. It was 4 by 2 by 1 cm. in size. The fallopian tubes and ovaries were atrophic. There was a fibromyoma 1 cm. in diameter in the right ovary.

CASE 2.—A single woman, aged forty-one years, came to the clinic because of continuous spotting of blood from the vagina, which had been present for eighteen months. There was no family history of carcinoma. Prior to the onset of the present symptoms, her menstrual periods had been perfectly normal in amount and had occurred regularly. Eighteen months before she came to the clinic, her menses

had been marked by excessive bleeding and passage of clots. After this, she had lost just a small amount of blood a day, enough to necessitate the constant wearing

Fig. 1.—Gross specimen from Case 1 showing the carcinoma involving the internal os and another carcinoma at the left uterine horn.

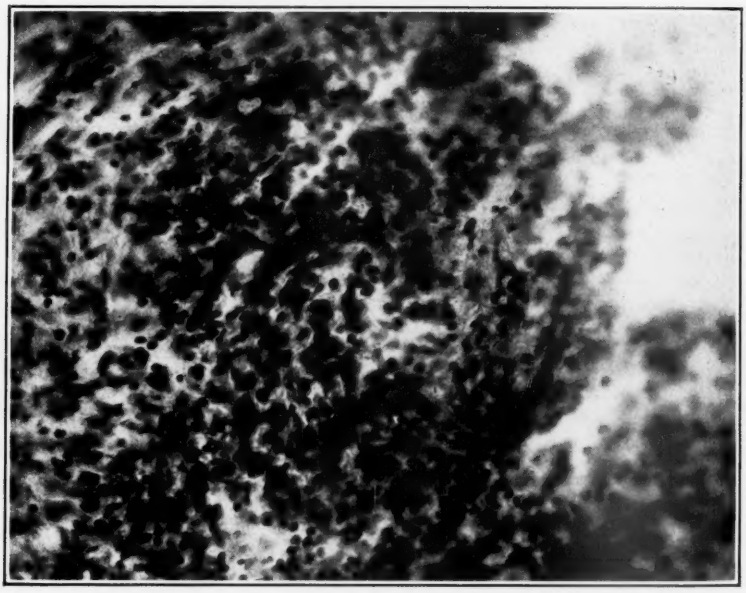

Fig. 2.—Section of the squamous cell epithelioma, Grade 3, at the internal os (×275).

of a pad. A year ago, before she came to the clinic, excessive flow again had occurred. The intervening menstrual periods had been normal. Dilatation and curet-

Fig. 3.—Section of the adenocarcinoma, Grade 1, at the left uterine horn (×120).

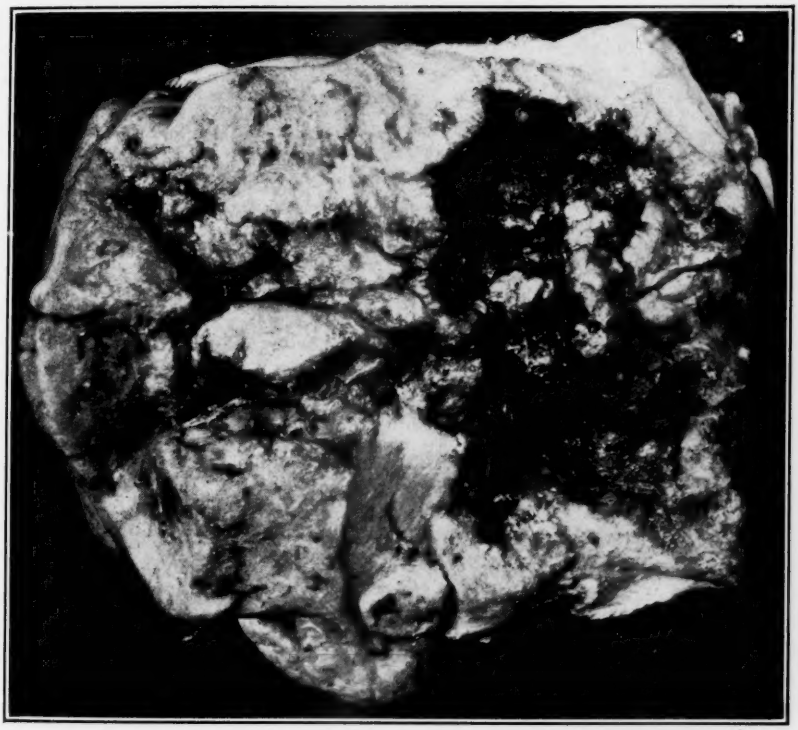

Fig. 4.—Gross specimen of the uterus from Case 2 showing a carcinomatous involvement of almost the entire uterus.

tage had been performed. The microscopic report had been polypoid endometrium. The operation had not altered the clinical picture, which had continued as stated, until five months ago, when menstrual periods had become longer than they had been

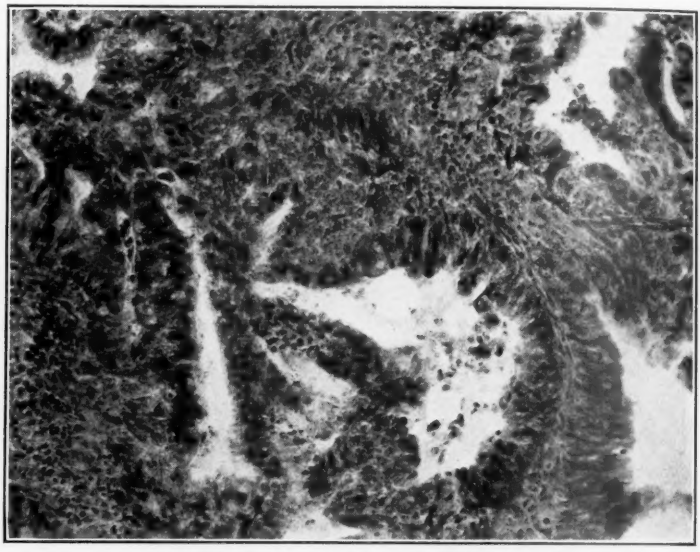

Fig. 5.—Section of adenocarcinoma, Grade 3, near the internal os of the uterus (×120).

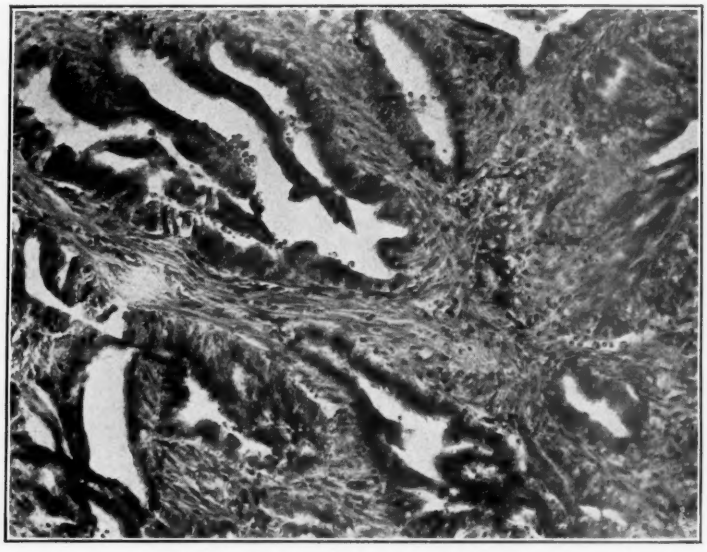

Fig. 6.—Section of adenocarcinoma, Grade 2, near the fundus of the uterus (×120).

and had lasted two weeks, and the intermenstrual bleeding had become more profuse than it had been. She had noted that a thin, watery fluid had been mixed with the bloody discharge, which had caused it to have a foul odor. Frequently, she had a cramplike suprapubic pain. For two months before she came to the clinic, the discharge had increased in amount and no regular periods had occurred.

Examination at the clinic revealed that she was a thin, anemic-appearing woman, who weighed 93 pounds (42.2 kg.). The significant findings relative to her symptoms were a large, irregular, and retroverted uterus; an enlarged cervix, which bled easily; and a mild secondary anemia.

The uterus was explored through a low midline incision. A firm lesion was palpated in the cervix, which felt like a cervical fibroid. There apparently was no induration of the broad ligament or involvement of the lymph nodes. A total abdominal hysterectomy, with bilateral salpingo-oophorectomy was performed. Her convalescence was somewhat prolonged by a bronchopneumonia which developed on the basis of a preexisting bronchiectasis of long standing. She was dismissed from the hospital in good condition.

A malignant mass, which measured 11 by 9 by 4 cm., was found (Figs. 4, 5, and 6). This involved practically the whole uterus, including the internal os of the cervix and the paracervical tissue. In the body of the uterus, the mass was an adenocarcinoma, Grade 2, while in the cervix it was an adenocarcinoma, Grade 3. Bilateral chronic cystic oophoritis and chronic salpingitis were found.

COMMENT

There can be no doubt of the double origin of the tumors in Case 1, as one was derived from the squamous epithelium and the other from the uterine glands. In Case 2, both tumors were derived from the uterine glands and were grossly indistinguishable. However, the distinct difference in the amount of differentiation of the cells between two regions of the tumors in the uterus leads us to believe that there is reason for designating them as two different malignant processes.

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Walther describes two cases of lymphosarcomatosis of the female genitalia which he studied and adds four from the literature. The growth started in the uterus in five and in the ovaries in the sixth case. Five tumors showed average maturity, the cells resembling lymphoblasts and lymphocytes. These tumors spread by infiltration into the surrounding structures followed by lymphogenic metastases to the retroperitoneal lymph nodes and finally to distant lymph nodes. Finally there was a hematogenous metastasis together with implantation growths. No leucemic changes were found in the spleen, marrow, liver or blood, thus ruling out systemic leucemias. These tumors all originated in preexisting lymphatic tissue.

The clinical picture of lymphosarcomatosis is similar to that of a carcinomatosis, except that the process is more malignant, more rapid, and results in death earlier. These tumors occur in women between the ages of forty-five and sixty-five years.

RALPH A. REIS.

TREATMENT OF AMENORRHEA*

II. Effects of Anterior Pituitary-Like Hormone from the Urine of Pregnant Women. Eleven Trials in Four Patients

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BECAUSE the anterior pituitary-like hormone from the urine of pregnant women stimulates the quiescent ovaries of intact, immature rats and mice to maturate and develop functioning follicles and corpora lutea (the Aschheim-Zondek reaction); and because the resting ovaries of intact, mature rabbits can likewise be stirred into similar activity, it has been thought by many[1] that this effect can be obtained in human beings in whom amenorrhea bespeaks inactive ovaries. To show that this does not always occur is the purpose of this paper.

When follicles become mature they secrete estrin which causes the endometrium to proliferate. When the corpus luteum is formed, progestin is elaborated. This further stimulates the endometrium, which thus develops into the so-called secreting, functional, or progestational phase. If the endometrium of a patient with amenorrhea atrophies or remains in an early resting condition, an absence or marked insufficiency of estrin may be assumed, and therefore, also, an absence of functioning follicles or a hypoplasia of such. If it remains in the proliferative phase, as is characteristic of those periods of amenorrhea interspersed with menorrhagia, which form the clinical entity, metropathia hemorrhagica, or dysfunctional uterine hemorrhage, it may be assumed that estrin is constantly present and therefore that an abnormally functioning follicle is present in the ovary. In such a condition of persisting proliferation in the endometrium without succeeding secretion, the absence of progestin can likewise be assumed, and, therefore, a failure of corpus luteum formation; for were this body present, its hormone would cause further development of the endometrium from the proliferative to the secretory stage. If, then, we know the condition of the endometrium, we may deduce the condition of the ovaries.

To test the assumption that pregnancy urine extract of anterior pituitary-like hormone would stimulate the ovaries of women with amenorrhea, as it does the ovaries of some laboratory animals, we obtained specimens of the endometrium by the suction curette[2] at various times during the amenorrhea of several patients, and other specimens before and after the

*We are grateful also to Dr. G. D. Krumbhaar for assistance in preparing this paper.

injection of the hormone on trial. Two commercial preparations of pregnancy urine hormone were used; antuitrin-S and follutein.*

Synopses of eleven trials in 4 patients follow:

CASE 1.—(No. 21283.) Patient aged twenty-eight, had had amenorrhea since the birth of a child two and one-half years before admission to the clinic on Oct. 14, 1932. Basal metabolism rate −6 per cent. October 17 to May 5, dried thyroid (Armour) gr. ii to v, each day. October 17 to January 23, antuitrin-S, 27 × 100 rat units. Feb. 3, 1933, biopsy: Atrophic endometrium. March 24, biopsy: atrophic endometrium.

Exper. 1.—May 5 to May 15, follutein, 5 × 500 rat units. May 12, biopsy: atrophic endometrium. May 26, biopsy: atrophic endometrium. June 2, biopsy: atrophic endometrium.

Exper. 2.—June 5 to June 16, follutein, 6 × 500 rat units. June 16, biopsy: very early proliferative phase. June 23, biopsy: very early proliferative phase. June 30, biopsy: very early proliferative phase.

Exper. 3.—June 30 to July 7, follutein, 4 × 500 rat units. July 7, biopsy: very early proliferative phase. July 10 to July 21, follutein 3 × 500 rat units. July 21, biopsy: atrophic endometrium. There was no staining at any time.

No sign of secretion was found in the endometrium after any treatment with pregnancy urine extract, which must have failed, therefore, to cause corpus luteum formation; furthermore, although it is only doubtful that the extract completely failed to stimulate even the follicles, it is clear that if it did at all they were not made to develop far enough to cause more than a very slight effect on the endometrium.

With this patient, after no series of treatments with pregnancy urine extract was there any sign of any bleeding. That these failures to stimulate the endometrium beyond the earliest proliferative phase were not due to an insensitivity or absent receptor quality on the part of the endometrium was clearly demonstrated by further experiments already reported.[2] In these this patient was twice given 5 × 10,000 rat units of progynon-B (Schering). After each series of 5 injections the endometrium was found to have developed to the ten-day type of proliferation. Ten days after the first series there occurred vaginal bleeding that lasted four days, and eight days after the second series again, bleeding occurred, requiring two napkins daily, for a few days. A third series of 5 × 10,000 rat units of progynon-B was given and followed by 5 × 10 rabbit units of proluton (Schering's preparation of progestin). After this a secreting endometrium was found and menstruation lasting three days followed on the day after the last dose of proluton.

CASE 2.—(No. 21258.) Patient was twenty-three years of age. Her periods had always been regular until marriage six years before admission to the clinic in January, 1933. For four years after she was married she experienced a steadily diminishing flow that stopped altogether two years before admission. She had gained 50 pounds in the first six months following marriage. Jan. 27, 1933, biopsy: atrophic endometrium. Jan. 28 to March 5, theelol 18,500 rat units. March 3, biposy: dysplastic eight- to ten-day proliferating endometrium. March 5, catamenia, five days, two napkins a day.

Exper. 4.—March 20 to April 4, antuitrin-S, 5 × 500 rat units. April 7, biopsy: atrophic endometrium. April 9, catamenia, five days, two napkins per day.

Exper. 5.—April 28 to May 3, antuitrin-S, 2 × 500 rat units. May 5, biopsy: fourteen-day proliferating endometrium. May 6, catamenia, two days, two pads a

*Parke, Davis & Co. generously supplied the antuitrin-S, and E. R. Squibb & Sons the follutein used.

day. May 5 to May 12, antuitrin-S, 3 × 500 rat units. May 22 to May 26, progestin, 3 × 2 rabbit units. May 25, catamenia one day. June and July, 1933, no treatment and no flowing. July 28, biopsy: atrophic endometrium. July 28 to Aug. 4, theelin, 2 × 500 rat units. August 4, biopsy: ten-day dysplastic endometrium. August 6, catamenia three days. August 8 to August 11, theelin, 2 × 500 rat units. August 11, biopsy: atrophic endometrium. August 17, patient flowed profusely for twenty-four hours and passed clots. September 1, biopsy: atrophic endometrium.

The results of the treatment here are confusing. After 37 × 500 rat units of theelol by mouth, the endometrium, as would be expected, had grown from the atrophic to the twelve-day proliferative stage. The patient flowed for five days, two napkins a day, beginning on the day of the last dose. It has been shown in monkeys that estrin will delay the onset of an expected flow while it is given, until, after long dosage the flowing mechanism escapes from the inhibition of the estrin and the delayed flow occurs. Werner and Collier[3] have likewise shown a similar phenomenon in castrated women who flowed while taking estrin. This is not unlike the mechanism of flow in women with dysfunctional uterine hemorrhage. Perhaps this explains the flow in this patient so soon after she had taken 36 × 500 rat units of theelol.

It might be noted, however, that the flow occurred two days after a biopsy. Fifteen days after that period began, a series of 5 × 500 rat units of antuitrin-S was started. A biopsy taken three days after the last dose revealed an atrophied endometrium; yet, nevertheless, flow, rquiring two napkins a day, began again two days after the biopsy, and lasted for five days. The following month after only 2 × 500 rat units of antuitrin-S the patient flowed slightly for two days after a biopsy showing a fourteen-day proliferating endometrium. A year later after only 500 rat units of theelin this patient flowed for three days, again two days after a biopsy which showed atrophy of the endometrium. On the day between the biopsy and the flow she had another 500 rat units of theelin. It must not be assumed that any flowing which occurred after antuitrin-S was induced by it, for it has been noted by several observers that instrumentation of the uterus may upset the existing endocrine situation in the human being as it always does in the mature isolated female rabbit, cat, and ferret. It is conceivable that such an interference is accountable for the twelve-day proliferation found on May 5, 1933, after only 2 × 500 rat units of antuitrin-S, though it could be argued that this was a late effect of the 5× 500 rat units of antuitrin-S given six weeks before. Such an effect was not found in the two trials with the previous patient, however, nor in the three trials with the following patient. At all events, this second patient, like the first, fails to show in her endometrium any corpus luteum effect after the injection of pregnancy urine extract. Once she showed an estrin effect after 2 × 500 rat units of antuitrin-S probably not due entirely to the possible stimulating effect of this hormone on the ovaries, but rather, perhaps, to the indirect effect of the cervical stimulation on her own anterior pituitary.

CASE 3.—(No. 21238.) Patient, aged twenty-seven, had had only 12 periods since she started to menstruate at the age of eighteen. Her last period before coming to the clinic, Jan. 20, 1933, had been on July 1, 1931.

Exper. 6.—March 13 to March 24, 1933, antuitrin-S, 3 × 500 rat units. March 24, biopsy: atrophic endometrium. April 21, biopsy: atrophic endometrium.

Exper. 7.—April 21 to May 5, antuitrin-S, 7 × 500 rat units. May 5, biopsy: atrophic endometrium.

Exper. 8.—May 19 to June 2, antuitrin-S, 7 × 500 rat units. June 2, biopsy: early proliferative phase. June 9, biopsy: resting endometrium. June 16, biopsy: resting endometrium. June 23, biopsy: resting endometrium.

Exper. 9.—October 13 to October 25, theelin, 6 × 500 rat units. October 27 to November 8, follutein, 6 × 500 rat units. November 17, biopsy: twenty-one-day mid-secretory endometrium. Following this there was no catamenia. December 4, biopsy: resting endometrium. February 18, 1934, stained one drop. April 20, biopsy: resting endometrium.

Exper. 10.—April 23 to May 2, progynon, 5 × 500 rat units. May 4, biopsy: twelve-day proliferating endometrium. May 4 to May 14, follutein, 5 × 500 rat units. May 16, biopsy: early proliferating phase. May 25 to June 8, progynon, 6 × 10,000 rat units. June 8, biopsy: eight- to ten-day proliferating phase. June 11, slight staining. June 11 to June 15, proluton, 5 × 1 rabbit unit. June 15, biopsy: atrophied endometrium. August 28, biopsy: atrophied endometrium.

Here again in two instances, on March 24 and May 5, 1933, we fail to find evidence in the endometrium of any appreciable effect on the ovary after antuitrin-S. The following month, June 2, after 6 × 500 rat units of antuitrin-S, we do find a six-day proliferation. No flowing supervenes, however, yet the week following, the endometrium is again found at a much earlier stage, similar to that commonly called atrophy. Perhaps here on June 2 we have a suggestion of stimulation, discounting the effect of biopsy instrumentation.

The experiment which followed, ending with a biopsy on Nov. 17, 1933, is very interesting. A twenty-one-day secreting endometrium is found after theelin followed by follutein. No flow follows, yet biopsy two weeks later shows regression to an atrophied or very early proliferating phase. Is this a single instance of corpus luteum formation by pregnancy urine hormone in 11 trials on these 4 patients? It is suggestive that in the same patient, Experiments 6, 7, and 8 all failed to produce any sign of corpus luteum formation. Experiment 9 differs from them in that follutein was used instead of antuitrin-S. These two products are generally considered by biologists as preparations of the same hormone, and to have similar effects in equal dosage. Experiment 9 also differed from the others in that this time the pregnancy urine extract was preceded by theelin. There is no experimental evidence nor is it theoretically likely that estrin sensitizes the follicle to the pregnancy urine hormone. In Experiment 10, progynon, an estrogenic preparation not biologically dissimilar from theelin, and closely related chemically, failed to do so, at least up to twelve days after the first dose and two days after the last dose of follutein.

The failure to flow during such a marked regression of the endometrium is a very unusual observation. Perhaps it occurs oftener than is suspected. We know that patients who customarily each month flow only for half an hour, barely staining one napkin, menstruate thus meagerly from a fully developed twenty-eight-day predeciduum, which in spite of the scant blood loss regresses to the normal early proliferating endometrium characteristic of the first six days of the cycle. The patient of the experiment may be but one stage down in the scale of bleeding. Nor is this failure to menstruate while the endometrium regresses from a full secretory to an early proliferating phase unthinkable. Except for the primates, it is the common occurrence in all other mammals in whom pseudopregnancy develops a deciduum which in time regresses without bleeding. Possibly such is the case in those patients with amenorrhea who become pregnant; and the explanation is not that they would have had a period two weeks after conception had they failed to become pregnant.

TABLE I. EFFECTS OF P.U. (A.P.L.) EXTRACT IN AMENORRHEA*

EXPERIMENT	CASE	AGE	DURATION OF AMENORRHEA	BIOPSY BEFORE	TREATMENT	BIOPSY AFTER	FLOW
1	109/122	28	2½ yr.	Atrophic endometrium	Follutein 5 × 500 R.U.	Atrophic endometrium	0
2	109/122	28	2½ yr.	Atrophic endometrium	Follutein 6 × 500 R.U.	Early prolif. endometrium	0
3	109/122	28	2½ yr.	Early prolif. endometrium	Follutein 6 × 500 R.U.	Atrophic endometrium	0
4	112/258	23	2 yr.	----------	Antuitrin-S 5 × 500 R.U.	Atrophic endometrium	5 days
5	112/258	23	2 yr.	----------	Antuitrin-S 5 × 500 R.U. Proluton 2 × 2 rabbit units	14-day endometrium	1 day
6	122/123	27	1½ yr.	----------	Antuitrin-S 2 × 500 R.U.	Atrophic endometrium	0
7	122/123	27	1½ yr.	Resting endometrium	Antuitrin-S 6 × 500 R.U.	Resting endometrium	0
8	122/123	27	1½ yr.	Resting endometrium	Antuitrin-S 7 × 500 R.U.	6-day proliferating endometrium	0
9	122/123	27	1½ yr.	----------	Follutein 6 × 500 R.U.	21-day secreting endometrium	0
10	122/123	27	1½ yr.	Resting endometrium	Progynon 5 × 5000 R.U. Follutein 5 × 500 R.U.	Early prolif. endometrium	0
11	114/ 55	33	1 yr.	----------	Antuitrin-S 3 × 500 R.U.	Resting endometrium	0

*NOTE: In only one of eleven experiments was a secreting endometrium found after giving pregnancy urine extract. In two cases flow followed the treatment, but was not clearly due to it (see text). Nor can a change from atrophic or resting endometrium to an early proliferating endometrium be surely attributed to the treatment for many patients with amenorrhea have an endometrium which varies within even wider limits because of slight autonomous ovarian activity.

CASE 4.—(No. 21526.) Patient, aged thirty-three, had had her last real period a year before admission to the clinic on March 16, 1933, although she had a little staining four months before.

Exper. 11.—March 16 to March 29, 1933, antuitrin-S, 3 × 500 rat units and follutein, 2 × 500 rat units. April 7, biopsy: resting endometrium. April 14, biopsy: resting endometrium. April 21, biopsy: resting endometrium.

Here once more we fail to obtain evidence of any good stimulation of the follicular apparatus by pregnancy urine extract, assuming that such follicular activity would cause changes in the endometrium characteristic of estrin and progestin.

SUMMARY

An attempt was made to detect in human beings an ovary-stimulating effect in anterior pituitary-like, pregnancy urine extract. To four married women, aged twenty-three, twenty-seven, twenty-eight, and thirty-three, with amenorrhea for one to two and one-half years, were given total doses of either antuitrin-S or follutein, varying in stated potency from 1,500 R. U. to 3,500 R. U. The individual dose was 500 R. U. given intramuscularly on alternate days (Table I). Biopsies of the endometrium were made sometimes before, sometimes during, and in each case after treatment. In only two instances was there any change in the endometrium which would suggest increased ovarian function. In only one case (Exper. 9) was the treatment followed by the appearance of a progestin-stimulated endometrium. There is some question, in even this one case, that the ovary was actually stimulated by the injections, as a repetition of the experiment failed to give a similar result. Three other experiments with this same patient were negative. In only two cases was there any flow following the treatment, and in one of them it was from an atrophic endometrium, in a patient whose flowing mechanism seemed very unstable during treatment with various hormones. (Case 2.)

CONCLUSION

From moderate doses of pregnancy urine extract, no ovary-stimulating effect can be detected in the endometrium of the human female with amenorrhea. Johnson[4] has likewise been unable to detect any such effect from pregnancy urine extract in monkeys, though much larger doses were given.

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THE INCIDENCE AND TREATMENT OF SECONDARY ANEMIA IN OUT-PATIENT MATERNITY PATIENTS*

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(*From the Service of the Lying-In Hospital*)

THE fact that the anemias of pregnancy, both primary and secondary, respond rapidly, and in some instances dramatically, to appropriate therapy has been conclusively demonstrated by the work of Strauss and Castle,[1] of Mettier and Minot,[2] and others. Since these advances, the extent of the obligation of obstetricians to their ward patients in this respect has become somewhat difficult of determination. We would not wish to neglect the treatment of serious anemias in the patients coming to our ward services for prenatal care and delivery, and at the same time we do not want to lay additional and possibly unnecessary burdens both of time and expense on the already overstrained prenatal facilities for ward cases. The taking of blood counts and estimation of hemoglobins is a meticulous, time-consuming business and, if not properly done, is valueless. If such study were to be incorporated as a routine part of prenatal care for all ward patients, an already elaborate regime would be greatly complicated, and the present-day burden of hospital expense would be aggravated. Would it not be safe to rely upon our clinical acumen and order such studies only on patients whose general appearance and symptoms were suggestive, as we have done heretofore? This presentation makes an attempt to answer these questions, and some other related problems. One of these is whether iron therapy is as highly effective when the patient is not in the hospital, and where lack of intelligence and of cooperation must be reckoned with. Not unimportant also is the question as to whether some more convenient form of iron therapy would be as effective as treatment with iron and ammonium citrate which heretofore has generally been accepted as standard. With this in mind, we decided to try the use of ferrous sulphate in tablet form, since recent reports in the literature[3, 4, 5] seem to indicate that from the point of view of dosage it is some ten times as potent in hemoglobin regeneration as iron and ammonium citrate, and more convenient of oral administration.

PROCEDURE

This study was made from ambulatory patients reporting for admission to the prenatal clinic of the Philadelphia Lying-In Hospital. No patient was included

*Presented before a meeting of the Obstetrical Society of Philadelphia, October 3, 1935.

in the series if her pregnancy was known to be complicated by any pathologic condition. Each new patient, after being interviewed by the financial clerk and accepted for hospital delivery, was referred to a special technician for a hemoglobin and red blood cell count. In this study a hemoglobinometer of the Sahli type was used. The instrument was checked at the start, and on several subsequent occasions, against another Sahli apparatus on which gas analysis standardization had just been performed. Double counts were taken on each patient and the average of the two was accepted as being correct. All the blood pipettes were new and were of the same standard. All the work was done by one special technician.

It may be stressed that in order to have blood work of this kind reliably performed it is absolutely essential to have a special technician in attendance at the Clinic. Little or no reliance can be placed upon red blood cell counts, or more

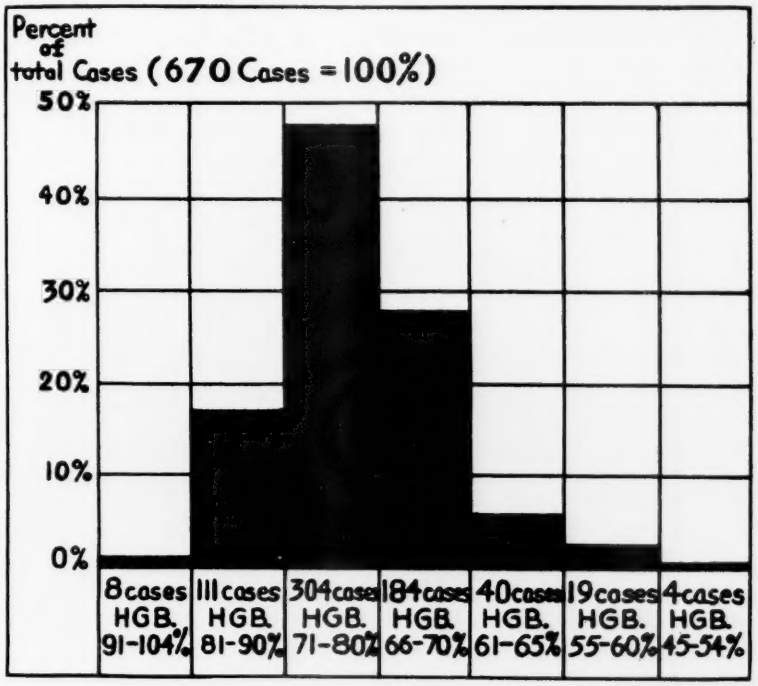

Fig. 1.—Hemoglobin estimation in a group of 670 pregnant women.

particularly upon hemoglobin readings, when they are done by constantly changing personnel, with unstandardized apparatus, in the hurry and bustle of large prenatal clinics.

All new maternity patients reporting to the Clinic had blood examinations done as described. All patients who had a hemoglobin of 65 per cent or less were regarded as needing treatment, unless they were four weeks or less from term. If treatment was needed, the patient was given either (a) iron and ammoniun citrate, 25 per cent solution, and instructed to take two teaspoonfuls three times a day (total dosage 90 gr. a day), or (b) 3 gr. of ferrous sulphate tablets* four times

*The 3 gr. ferrous sulphate tablets used in this series were obtained through the courtesy of Smith, Kline and French Laboratories, Philadelphia, Pa.

a day (total dosage 12 gr. a day), or (c) tablets containing an inert substance. The last group was used as a control. Both patients and controls were instructed to report to the special technician at weekly intervals for blood counts and hemoglobin readings. They were questioned at such visits about the symptoms produced by the medication, and were encouraged to be regular in taking their treatment.

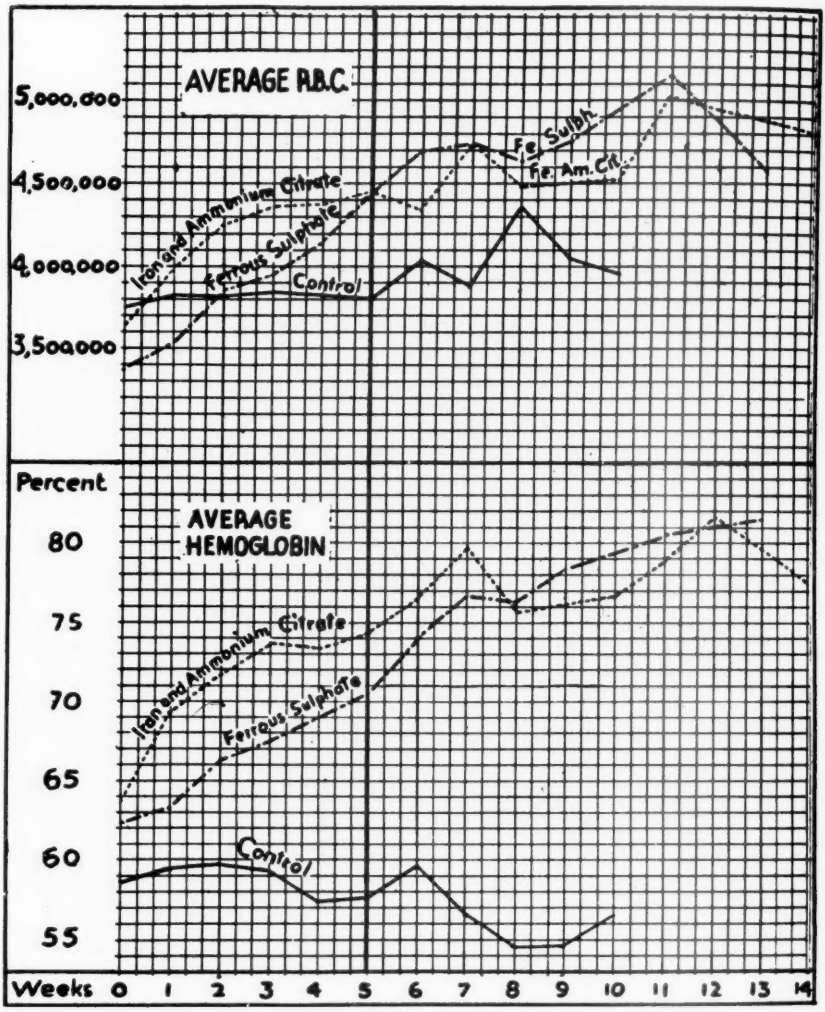

Fig. 2.—Charts showing the average rise in R.B.C. and Hg in the three groups.

RESULTS

As the study progressed, it became apparent that the incidence of marked secondary anemia in pregnancy was comparatively rare. A total of 670 patients were examined in which only 63 patients had hemoglobin readings of less than 65 per cent (Fig. 1). In the group of 63 patients whose blood findings showed that treatment was indicated, there were 7 patients seen too late for treatment, and 29 who for some reason or another were unable or unwilling to cooperate to a sufficient

degree to be included in this series. This left only 26 patients who were available for study. Of these, approximately 63 per cent had hemoglobins ranging between 65 per cent and 60 per cent. Of the remaining 37 per cent, only four patients had hemoglobins lower than 55 per cent, 48 per cent being the lowest figure recorded in the entire group. No anemias of primary type were observed.

In the twenty-six patients who cooperated, and even in this group one is far from certain of 100 per cent cooperation, eight were given iron and ammonium citrate, twelve were given the ferrous sulphate tablets, and six were used as controls. The results are shown in Fig. 2. The graphs cover the entire period of study, but it may be remarked that after the fifth week of treatment, the averages are much less significant, since the number of patients reporting decreased steadily due to delivery intervening.

It will be observed that the red blood cell count closely paralleled the hemoglobin readings. There was a moderate but clear-cut response to medication in hemoglobin and red blood cell regeneration in the patients treated with iron and ammonium citrate, and ferrous sulphate. While the actual figures show a somewhat greater hemoglobin rise by the fifth week for the patients receiving iron and ammonium citrate, the increase in red blood cell count during the same period was greater with those treated with the ferrous sulphate. There seems to be no significant difference in the results of the two forms of iron therapy. The control group showed no significant increase either in hemoglobin or in red blood cell regeneration. Complaints as to diarrhea, gastric upset, and abdominal cramps were not serious with either form of medication. The patients showed a preference for ferrous sulphate because it did not "taste bitter."

SUMMARY AND CONCLUSIONS

1. Anemia of primary type does not occur frequently enough in pregnancy to constitute a real hazard to maternal health, no cases being observed in a series of 670 pregnant women.

2. Grave secondary anemia is relatively infrequent in pregnancy, only 4 patients with hemoglobin readings of under 55 per cent occurring in our series.

3. Although all anemic cases were offered iron therapy free of charge, and encouraged to be faithful in taking the medication, less than half (42 per cent) showed sufficient cooperation to render treatment effective.

4. There was a clear-cut rise in hemoglobin and red blood cell count in the patients who reported having taken iron therapy regularly.

5. In the control group there was no significant rise in red blood cell count or hemoglobin.

6. Ferrous sulphate in one-eighth the dosage is equally as effective as iron and ammonium citrate, in the treatment of secondary anemia in pregnancy. Adequate dosage for ferrous sulphate is considerably cheaper and more convenient for the patient.

7. In general we feel that routine blood cell count and hemoglobin estimations on all ward prenatal patients, as an integral part of the initial physical examination, are hardly worth the time and expense involved, and such studies should be reserved for cases whose clinical pictures warrant it.

8. Inasmuch as 36 per cent of the patients in this series showed hemoglobins below 70 per cent, we recommend that all maternity patients be routinely instructed to take 3 gr. ferrous sulphate tablets four times a day, during the last two months of pregnancy.

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DISCUSSION

DR. THOMAS FITZ-HUGH, JR.—In the last ten years there has been a great revival of interest in iron therapy, with a return to the old advice of massive dosage. Accordingly we have learned that it takes about 100 gr. of ferric ammonium citrate per day for an adult to produce optimum hemoglobin regeneration (i.e., about 1 per cent increase of hemoglobin per day from a low level to a nearly normal level). The reason for this relatively tremendous requirement had not until recently been satisfactorily explained. The answer now appears to reside in the fact that only the ferrous form of iron is absorbable and utilizable in hemoglobin regeneration.

In order to produce enough ferrous iron to be effective, we have to give a large amount in the form of ferric iron. Only that portion which is reduced to ferrous form is useful. The experience of my Clinic, recently reported in detail by Dr. Clara Davis, shows results quite like those of Dr. Toland's. We have found that ferrous iron in the form of ferrous sulphate is equally effective in about one-eighth to one-tenth of the dose of ferric ammonium citrate, that it is easier to take, that it is usually better tolerated, and that it is more economical. One can maintain a patient on adequate iron therapy in the form of ferrous sulphate pills, for less than $1.00 a month.

The concept of a conditioned deficiency is, I think, a very useful and fruitful one, introduced into clinical medicine by Dr. William Castle. An example of the conditioned deficiency is the following: A person may have a reasonably adequate intake in general and yet develop a deficiency, the basis being some gastrointestinal "conditioning" factor which prevents proper absorption, or promotes excessive excretion, or interferes with normal storage of the interaction products of digestion with the food factors. The pregnant woman presents a rather ideal "set-up" for the development of conditioned deficiencies. Castle has shown that there is progressive failure of gastric secretory power through pregnancy in a fair percentage of women.

On this basis we would expect the development of deficiencies in substances for which the normal gastric juice is necessary for the extraction from the food of adequate material. Iron is one such substance and others are iodine, calcium, certain vitamins and the substance whose lack produces pernicious anemia. The resulting fact is that there are many cases of conditioned iron deficiency type (the so-called anemia of pregnancy), an occasional case of the so-called "pernicious anemia" type of pregnancy-conditioned deficiency, as well as disturbance of calcium and iodine, and vitamin metabolism.

In Dr. Toland's presentation, the incidence of fairly severe secondary anemia is a little lower than the average statistics, and his failure to find a single case of macrocytic or "pernicious" anemia is perhaps a little unusual, although the latter is admittedly rare.

THE RÔLE OF THE AMNIOTIC SAC IN LABOR*

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WITHIN the past two years there have been increasingly numerous references to the efficacy of artificial rupture of membranes for the induction of labor. Furthermore, statements have been made that this method is not only effective, but harmless, both as regards the mother and the child. That the effect upon the duration of labor is to shorten it, is the consensus of opinion among recent writers on the subject.

Margaret Schultze,[1] in a study of 600 cases of spontaneous premature rupture of membranes, found primiparous labors to average 12.1 hours, and multiparous labors to average 7.1 hours. She also found that in two-thirds of the operative deliveries for dystocia, there were one or more causes for the dystocia aside from dry labor. A maternal morbidity of 17 per cent occurred in her series, the standard used being an elevation of postpartum temperature to 100.4° on one or more occasions. Norris[2] reported a maternal morbidity of 20 per cent in his series of premature rupture of membranes. In Morton's[3] series the average duration of labor was 9.6 hours for primiparas and 3.9 hours for multiparas. Mason[4] reported 9.5 hours for primiparas and 6.9 hours for multiparas and stated that the proportion of long labors in cases of premature rupture of membranes is less than in cases where the membranes remain intact until the cervix is fully dilated. Fitzgibbon[5] has stated that the bag of waters does not play any part in the dilatation of the cervix. A duration of labor of 11.2 hours in primiparas and 7.0 hours in multiparas following premature rupture of membranes was reported by Jackson.[6] All of these writers, including Guttmacher and Douglas,[7] agreed that there was no increase in maternal morbidity. The latter authors also reported a decrease in length of labor following artificial rupture of membranes to 10.5 hours for primiparas and 5.4 hours for multiparas. In their series the fetal mortality for term babies was 5.08 per cent, which is about the same as their general fetal mortality at term. King[8] stated that the dystocia credited to dry labor is generally due to other complicating abnormal conditions, premature rupture of the membranes being a result rather than a cause of difficulty in labor.

Because the formerly accepted belief in hazards of dry labor seemed definitely contradicted by the writers quoted above, it was decided to investigate whether or not the fear was justified by our experience. Accordingly, a study was made of one thousand consecutive deliveries at Harper Hospital between January, 1934, and April, 1935. Only normal full-term single pregnancies with vertex presentations were used, there being 478 primiparas and 522 multiparas. The series was divided into two groups, one with spontaneous and the other with artificial rupture of the membranes. The groups numbered 734 and 266 respec-

*Read before the Detroit Obstetrical and Gyncological Society, October 1, 1935.

tively. In the group of 734 cases with spontaneous rupture of membranes there were 215 primiparas and 211 multiparas in whom the membranes ruptured either before or during the first stage of labor, and there were 148 primiparas and 160 multiparas with second stage rupture of the membranes. In the group of 266 patients with artificial rupture of the membranes, there were 52 primiparas and 68 multiparas with rupture either before or during the first stage of labor, and 63 primiparas and 83 multiparas in whom the membranes were ruptured after onset of the second stage of labor.

Included in the group of artificial rupture of the membranes were 59 patients in whom the membranes were ruptured for the induction of labor, and of these there were 20 primiparas and 39 multiparas. These 59 patients were studied separately in order to compare them with the whole group having artificial rupture of the membranes at various stages during labor.

The whole series was studied with regard to the length of labor as influenced by the time of rupture of the membranes and according to spontaneous or artificial rupture. The incidence of postpartum temperature elevation was noted, reading of 100.4° or over from any cause for any length of time being recorded as a temperature elevation. The effect of rupture of the membranes on the incidence of operative delivery was also noted, and the results of these studies are shown in Tables I to III.

TABLE I. LENGTH OF LABOR AS INFLUENCED BY THE TIME AND CAUSE OF RUPTURE OF MEMBRANES

		PRIMIPARAS	MULTIPARAS
A. Spontaneous rupture	First stage	11.49 hr.	5.92 hr.
	Second stage	14.19 hr.	5.96 hr.
B. Artificial rupture	First stage	14.04 hr.	5.63 hr.
	Second stage	13.35 hr.	7.13 hr.

It is apparent that these figures on the average length of labor, regardless of the time or cause of rupture of the membranes, are considerably less than the figures given by Williams[9] for a large series of spontaneous labors at Johns Hopkins Hospital, namely, eighteen hours for primiparas and twelve hours for multiparas. The writers quoted above called attention to the fact that their cases in which labor was induced by rupture of the membranes had a much shorter labor than eighteen and twelve hours. The figures in our series bear this out, but it is also noteworthy that the group with spontaneously ruptured membranes also had shorter labor. Moreover, the shortening of labor in all groups of our series was probably due, in part at least, to the relatively high incidence of operative delivery after complete dilatation of the cervix.

In Table II is given the incidence of temperature elevation for the several groups. Attention is again directed to the fact that these figures represent all puerperia with temperature elevation of 100.4° and over one or more times and is a more exacting standard than that

TABLE II. EFFECT OF RUPTURE OF MEMBRANES ON POSTPARTUM TEMPERATURE ELEVATION

A. Spontaneous rupture	Primiparas	1 in 4.7	21%
	Multiparas	1 in 8.2	12%
B. Artificial rupture	Primiparas	1 in 4.1	24%
	Multiparas	1 in 10.7	9%

of the American College of Surgeons. It is evident that the incidence of temperature elevation in primiparas is approximately twice that in multiparas, and that the incidence where the membranes have been ruptured artificially is about the same as in those with spontaneously ruptured membranes. This confirms the opinions of previous investigators that artificial rupture of the membranes does not increase maternal morbidity. The higher proportion of temperature elevations in primiparas may be due to the higher incidence of operative delivery.

TABLE III. EFFECT OF RUPTURE OF MEMBRANES ON OPERATIVE DELIVERY

		NO. OPER. DEL.	INCIDENCE	PERCENTAGE
A. Primiparas	Spontaneous rupture	204	1 in 1.7	56
	Artificial rupture	73	1 in 1.5	63
B. Multiparas	Spontaneous rupture	71	1 in 5.2	19
	Artificial rupture	32	1 in 4.7	21

The figures in Table III indicate that there is a slight increase in the incidence of operative delivery in cases where the membranes were ruptured artificially, but because of the relatively small number, it is not believed that this increase is sufficient to be particularly significant. Table IV shows that the preponderating form of operative delivery is by low forceps.

TABLE IV. TYPES AND NUMBER OF OPERATIVE DELIVERIES

		LOW F.	MID F.	V. & E.
A. Primiparas	Spontaneous rupture	183	15	8
	Artificial rupture	57	4	12
B. Multiparas	Spontaneous rupture	61	7	3
	Artificial rupture	21	6	5

It will be noted that in artificial rupture of the membranes, both for primiparas and multiparas, the incidence of version and extraction is considerably higher than in spontaneous rupture of the membranes. In a number of instances the membranes were ruptured artificially at the time of version and therefore this was not a causative factor in the indication for intervention. It is probable that these cases account

for the small increase in the total incidence of operative delivery in the group where the membranes were ruptured artificially.

TABLE V. A COMPARISON BETWEEN THE SPECIAL GROUP WITH RUPTURE OF THE MEMBRANES FOR INDUCTION OF LABOR AND THE WHOLE GROUP WITH ARTIFICIAL RUPTURE OF MEMBRANES

	WHOLE GROUP		SPECIAL GROUP	
	PRIMIPARAS	MULTIPARAS	PRIMIPARAS	MULTIPARAS
Length of labor	13.69 hr.	6.38 hr.	10.25 hr.	4.00 hr.
Temperature elev.	24%	9%	20%	15%
Incidence oper. del.	63%	21%	76%	23%
Percentage low for.	78%	65%	85%	88%
Percentage midfor.	6%	19%	10%	0
Percentage V and E.	12%	16%	5%	12%

A comparison of the special group of 59 cases in which the membranes were ruptured artificially before the onset of labor and the whole group of cases where membranes were ruptured artificially is shown in Table V. It is apparent that the figures for the group of cases in which the membranes were ruptured before the onset and for the induction of labor closely parallel those for the total group where the membranes were ruptured artificially regardless of the stage of labor. The length of labor in the special group was a little shorter and the incidence of temperature elevation and operative delivery about the same. The percentage of low forceps operations in relation to midforceps and version was a little higher.

The fetal mortality in the group of 59 cases in which the membranes were ruptured for the induction of labor at term consisted of one stillbirth, a percentage of 1.7. This is almost identical with the general full-term fetal mortality at Harper Hospital for the year 1934 or 1.6 per cent. It appears, therefore, that deductions made from a study of the whole group of cases in which the membranes were ruptured artificially are not invalidated because of the variance in time of rupture of the membranes. Nor is there evidence here that artificial rupture of the membranes for induction of labor subjects mother or child to any additional danger.

SUMMARY AND CONCLUSIONS

Recent literature on the subject of artificial rupture of the membranes indicates that it is an efficient method for the induction of labor, that it shortens labor to approximately ten to twelve hours for primiparas and five to seven hours for multiparas, that maternal morbidity and fetal mortality are not increased by the procedure and that it is not a cause of dystocia.

One thousand consecutive cases of normal full-term pregnancies with vertex presentation were studied with reference to:

1. The time and cause of rupture of the membranes, showing that in primiparas with spontaneous rupture of the membranes the average

length of labor was 12.9 hours and in multiparas 5.9 hours. In artificial rupture of the membranes, the average duration of labor was 13.6 hours in primiparas and 6.3 hours in multiparas, thus it appears that rupture of membranes does not seriously affect length of labor in primiparas or multiparas. Artificial rupture of membranes (either in first stage or second stage) does not result in prolongation of labor, neither does it expedite labor.

2. The effect on postpartum temperature elevation, showing that the incidence of temperature elevation to 100.4° F. on one or more days is no greater following artificial rupture of the membranes than following spontaneous rupture, the average incidence for both being 16 per cent; and that elevated temperatures were noted more frequently following delivery of primiparas than multiparas. The higher incidence of operative delivery (all forms) may account for increased incidence of temperature elevation in primiparas regardless of cause and time of rupture of membranes.

3. The effect on the incidence of operative delivery, showing that in both primiparas and multiparas the incidence of operative delivery is essentially the same regardless of time or cause of rupture of membranes.

4. The effect on the incidence of fetal mortality following artificial rupture of the membranes for induction of labor, showing that it is not increased, the percentage being 1.7 as compared with 1.6 per cent for all cases considered. The findings of this investigation substantiate our clinical impression that textbook figures for length of labor (in primiparas and multiparas) are in need of revision.

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The author states that a common cause of backache in multiparous women is malposition of the pelvis resulting in ligamentous and muscle strain. Complications such as ligamentous hypertrophic arthritis of the small joints, migration of the nucleus pulposus, and horizontal sacrum, follow some uncorrected cases. The treatment stresses rest in bed. Exercises such as clasping the flexed knees against the chest with the purpose of shortening the abdominal muscles and correction of the anteverted position of the pelvis, heat, massage, and correction of abnormal body weight prove effective.

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HEMOGLOBINURIA AS A SYMPTOM OF RUPTURED ECTOPIC PREGNANCY

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FORTUNATELY in a typical case of ruptured ectopic pregnancy, the history, symptomatology, and findings on examination are usually plainly indicative of the diagnosis. Still, in no small number of instances, in which the story and findings are less revealing, the problems of differential diagnosis assert themselves and frequently require a more exhaustive study to determine the true pathology. If what Robertson[1] says, "Hemoglobinuria will follow hemorrhage anywhere in the body," were true and generally known, then one might certainly expect to find in the medical literature an almost axiomatic relationship between hemoglobinuria and the hemoperitoneum which so frequently accompanies ruptured ectopic pregnancy. Although this relationship had doubtless not escaped the attention of numerous observers, there is a striking lack of emphasis or even mention of this correlation in many of the popular textbooks and journals of medicine.

So manifest was the occurrence of hemoglobinuria in a recent case of ruptured ectopic pregnancy that it seemed deserving of report. The apparent rarity of such a phenomenon also led to a more careful search for the presence of occult hemoglobin in cases showing no gross evidence of this pigment in the urine. It is not our purpose here to review all of the sparse literature on this subject, but rather to cite several publications and to present three cases with renewed emphasis on the study of the presence of hemoglobin in the urine.

For long it had been known that the intraperitoneal infection of foreign blood would cause hemoglobinuria as was shown by Nikolski in 1880.[2] Michaelis in 1901[3] reported a theretofore unmentioned form of hemoglobinuria in a patient having a ruptured ectopic pregnancy. That certain types of jaundice and hemoglobinemia may be etiologically related is apparent when one considers the liberation of pigments following extensive destruction of red blood cells. Thus Schottmüller[4] described jaundice, hemoglobinemia, and hemoglobinuria following the rupture of an ectopic pregnancy. He was enabled to diagnose correctly a questionable case of ruptured ectopic pregnancy on the basis of icterus, the jaundice appearing twenty-four hours after the hemorrhage. An excellent account of the genesis of jaundice associated with the hemorrhage from a ruptured ectopic pregnancy is given by Norris.[5] DeLee[6] has also mentioned the presence of hemoglobinemia following rupture of an ectopic pregnancy, particularly in the presence of jaundice. Da Costa[7] regarded hemoglobinuria as resulting from extreme cases of hemoglobinemia. It, however, remained for Whipple and his associates[8, 9] to demonstrate experimentally the actual renal threshold of hemoglobin introduced into the circulation.

CASE REPORTS

CASE 1.—A.Di P. (No. 51164). A thirty-four-year-old para v presented herself with a complaint of intense pain of six days' duration in the L.L.Q., radiating to the back and down the inner surface of the left leg. The onset of the pain was sudden and was shortly followed by pallor, rapid pulse, and a feeling of coldness and intense weakness. Three days later the urine became "wine colored." There was no dysuria or urinary frequency. On the following day her skin became jaundiced. Her last menstrual period had occurred three weeks prior to the onset of her symptoms and was atypical in that it lasted only five days instead of the usual seven days. The preceding menstrual period had occurred twenty-nine days earlier and was normal. She came from healthy familial stock, and aside from chronic constipation, she had enjoyed good health prior to her present complaint. Careful inquiry failed to elicit a history of malaria, hemorrhagic diathesis, recent chilling, or of previous jaundice or noteworthy pigmentation of the urine.

Examination showed the patient to be in profound systemic shock. The skin and conjunctivae were moderately jaundiced. Mucous membranes were pale. Blood pressure was 98/60. There was evidence of blood loss, with intraabdominal fluid. Diffuse tenderness was noted in the entire abdomen, particularly in the left lower quadrant. No masses were felt and there was no muscle spasm. No blood was noted in the vagina. The cervix was slightly patulous. The uterus could not be well outlined due to tenderness and obesity, but did not appear to be enlarged. Diffuse fullness but no mass could be felt in the culdesac of Douglas. Palpation of the left adnexal region caused intense pain.

Laboratory Findings.—R.B.C. 2,730,000; Hb. 50 per cent; W.B.C. 11,600, with 82 per cent polymorphonuclear leucocytes. Icteric index 21. Wassermann negative. A catheterized urine specimen was clear but mahogany red in color, specific gravity 1.016; reaction, faintly acid to litmus; albumin trace; sugar 0; acetone 0. The sediment contained a not abnormal number of white blood cells and epithelial cells. Rare red blood cells and no bacteria were found. The urine gave a strongly positive reaction to the guaiac and benzidine tests. Spectroscopically, the absorption bands of hemoglobin were plainly conspicuous.

The diagnosis of ruptured ectopic pregnancy was verified at laparotomy. The peritoneal cavity contained 600 c.c. of fresh and clotted blood. This was removed, and a left salpingo-oophorectomy was performed. The rupture had occurred near the fimbriated end of the tube, and below the site of rupture, early placental tissue was found on microscopic examination. The urine contained grossly recognizable hemoglobin for two days following operation. Spectroscopically, it could, however, still be identified two days longer. At this time the jaundice had disappeared, and blood examination showed icterus index of 5, nonprotein nitrogen 31 mg. per cent. After an uncomplicated twenty-one-day postoperative hospital stay, the patient was discharged in excellent condition. She was seen twice after her discharge from the hospital, and on neither occasion, the last one being five months after operation, did the urine contain demonstrable hemoglobin.

CASE 2.—D. L. (No. 66730). This twenty-one-year-old nullipara was admitted because of pain of three weeks' duration in the right lower abdominal quadrant. The pain began shortly after medical and instrumental attempts were made to bring on an abortion. At that time she had passed an expected menstrual period by two weeks. The preceding menstrual periods had been normal. The onset of pain in the right lower quadrant was accompanied by a brownish vaginal discharge, which became frankly bloody several days later. On the day of admission the patient was seized by intense pain in the right lower quadrant. There was nausea and vomiting. The patient felt dizzy and faint, and was hurried to the hospital.

Physical Examination.—The patient appeared undernourished. Temperature, pulse, and respiration were normal. The abdomen showed diffuse tenderness, most marked in the right lower quadrant, along with true muscular spasm. The vagina contained fresh blood. The uterus could not be outlined because of tenderness. In the culdesac a large, soft, tender mass was felt.

Laboratory Findings.—Wassermann negative. W.B.C. 28,900. Urine: clear, acid, sp. gr. 1.020; albumin faint trace; glucose 0; sediment, normal. Gross hemoglobin 0. Spectroscopic examination showed the typical absorption bands of hemoglobin.

At the time of examination, the diagnosis of postabortal pelvic abscess seemed likely. However, shortly after the pelvic examination the patient went into shock. The blood pressure fell rapidly from 110/70 to 85/40. Pulse rose from 72 to 126.

A posterior colpotomy was performed with escape of blood. At laparotomy the diagnosis of ectopic pregnancy, with tubal abortion, right, was established. The fresh and old blood, amounting to some 400 c.c. in all, was aspirated, and the right tube was removed.

Laboratory findings on the second postoperative day: R.B.C. 3,560,000; Hb. 9.6 gm. per cent. Icterus index 5. No hemoglobin could be detected on spectroscopic examination of the urine. The postoperative course was unremarkable, and the patient was discharged on the fourteenth day.

CASE 3.—M. McC. (No. 100016). This thirty-year-old nulliparous woman was admitted to the hospital three and a half hours after the onset of intense pain in the lower abdominal and epigastric regions. There was no nausea or vomiting. The menstrual periods had always been very irregular, the interval varying from three to eight weeks. Her last menstrual period had occurred five yeeks prior to the present illness. Slight vaginal spotting occurred on the day preceding admission. When examined, the patient was very pale and showed evidence of critical shock. Blood pressure was 60 systolic. The pulse at the wrist was imperceptible. The abdomen was diffusely tender. A tender bulging mass occupied the culdesac. The uterus was exquisitely tender on motion. The appendages were not outlinable due to pain.

Laboratory Findings on Admission.—R.B.C. 4,700,000; Hb. 12 gm. per cent; W.B.C. 28,900. Examination of a catheterized specimen of urine disclosed no albumin, blood, or spectroscopically recognizable hemoglobin. At laparotomy, which was immediately performed, the abdominal cavity was found to contain 800 c.c. of fresh blood which issued from a ruptured tubal pregnancy. Right salpingectomy was performed. On the first two days following operation the urine contained hemoglobin, demonstrated by the spectroscope. Thereafter, none was noted. The postoperative course was entirely satisfactory and the patient was discharged on the sixteenth day.

COMMENT

In Case 1, the diagnosis of ruptured ectopic pregnancy with massive intraabdominal hemorrhage was apparent. The jaundice and hemoglobinuria appear to have been definitely associated with the disease entity. In Case 2, the history of an attempted abortion confused the issue. The picture was compatible with the diagnosis of either pelvic inflammation with abscess formation or an ectopic pregnancy. The presence of hemoglobinuria before operation and its absence afterward may be explained on the basis of a fall of the level of hemoglobinemia at the time of operation, with subsequent failure to cause spilling over

through the kidneys following operation. In Case 3, it would appear that the recent onset of the hemorrhage did not permit enough time for absorption of the blood pigment at the time of urinalysis for hemoglobin just prior to operation.

In cases in which the diagnosis of ruptured ectopic pregnancy was established after the matter of hemoglobinuria had come to our personal attention, we have been able to demonstrate the pigment in the urine in four out of nine cases tested prior to operation. In one of these failures the history and physical findings had been rather confusing. The patient finally submitted to laparotomy because of persistence of symptoms that had been attributed to pelvic inflammation. About 40 gm. of old blood clots enmeshed in the omentum, but no fresh blood, were found. Urine examination had been negative. Doubtless, the amount of absorbed hemoglobin was well below the renal threshold level and consequently did not appear in the urine.

Norris clearly established the causal relationship between jaundice and certain cases of ruptured ectopic pregnancy, viz.: (1) The presence of free blood in the peritoneal cavity; (2) forthwith the development of jaundice; (3) the disappearance of the jaundice with the removal of the blood from the peritoneal cavity. Such a logical sequence and deduction might well also apply to the development of a hemoglobinuria. In the production of hemoglobinuria various interrelationships enter. Certainly the size and site of the hemorrhage are all important factors. Shortly after blood is shed and touches the peritoneal surface, it coagulates, according to DeLee, and is surrounded by a layer of fibrin. Under favorable circumstances, adhesions form and the blood becomes encapsulated. Absorption is impeded and the blood is more or less shielded against the action of lytic substances. Schottmüller hypothesized that autolysins might destroy the escaped red blood cells, with release of the hemoglobin. A similar view has also been expressed by Da Costa. The extravasated blood, according to Norris, is attacked not only by hemolysins, but in addition by proteoses and leucocytes. Hertzler[10] found that absorption of blood injected into the peritoneal cavity begins in four hours. Now, if the extravasated blood is rapidly broken down in the abdominal cavity, it is readily surmisable that its end-products are also quickly absorbed and disseminated throughout the body. The renal threshold, if exceeded, will permit the hemoglobin to escape in the urine. Smaller amounts can perhaps be demonstrated spectroscopically in the serum.

Whatever may be learned concerning the ultimate cause of hemoglobinuria, the consequential fact remains that it may be a not infrequent, and oftentimes a valuable, sign in the differential diagnosis of ruptured ectopic pregnancy.

SUMMARY

Hemoglobin in the urine would be more frequently encountered if one would search for it. The importance of chemical and spectroscopic tests is stressed. Hemoglobinuria is a not infrequent accompaniment of ruptured ectopic pregnancy with intraadbominal hemorrhage, and may be a significant symptom of the disease. Therefore, whenever the possibility of a ruptured ectopic pregnancy is considered in the differential diagnosis, the appearance of hemoglobinuria should be determined and evaluated in the presenting syndrome.

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TREATMENT OF SENILE VAGINITIS WITH ESTROGENIC HORMONES

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THE effect of the ovarian hormone on the vaginal mucosa has been shown in animals both immature and adult.

Stockard and Papanicolau[1] first described the cyclic changes occurring in the vaginal mucosa in immature rodents under the stimulation of estrogenic hormones. Allen[2] demonstrated that estrin when injected into immature monkeys caused vast proliferation of the layers of vaginal mucosa. Mazer and Ziserman[3] demonstrated that injections of estrin in spayed rodents produced growth and vascularity of the uterus and the vagina.

Davis and Hartman[4] studied the cyclic changes in the vagina in monkeys and found that the epithelium attains its greatest thickness in the midinterval, consisting at this time of an active basal layer, an inactive functional layer, and an intraepithelial zone of cornification interposed between these two which is called Dierks' layer. Following ovulation, desquamation begins and proceeds by a crumbling away of the functionalis which is usually not completely destroyed. Mitosis begins in the basalis on the first day of menstruation, becoming most marked near the time of ovulation. A cessation of ovarian activity such as is seen in the menopause definitely alters these physiologic changes.

Papanicolau and Shorr[5] showed that the injection of ovarian follicular hormones in women with ovarian deficiency following oophorectomy or menopause caused the

formation of cornified squamous cells in vaginal smears. These cells disappeared a few days after cessation of injection.

These vaginal changes have been utilized by Kaufman[6] in the treatment of vaginal ulceration due to hormone disturbance. Lewis[7, 8] has utilized the cyclical change in the vagina produced by injections of ovarian hormone in the treatment of gonococcal vaginitis in children. Brown,[9] and Te Linde and Brawner, Jr.,[10] have also reported favorably on the use of ovarian hormone in the treatment of vaginitis in children.

In order to determine whether the effect of these estrogenic hormones on the vagina would be of any value in the treatment of senile vaginitis, a series of twenty-five cases were placed under treatment with these substances.

The average age of these patients was fifty-one years, the youngest being forty-three and the oldest fifty-nine. They were all past the menopause. In the younger patients the menopause followed operations.

The chief complaints of these patients were a varying amount of whitish, rather thin vaginal discharge, with itching and a burning sensation in the external genitalia and vagina. Discharge was present in twenty-one of these patients, itching in eighteen, and burning sensation in thirteen. On examination the vulva was found to be atrophic and shriveled in the majority of patients; some presented reddening and hypertrophy of the labia, and in one patient the atrophy was associated with leucoplakia.

The vagina and the portio in every instance showed numerous small ulcerations, varying in size from a few millimeters to half a centimeter, stippling the mucosa.

The rest of the mucosa showed varying degrees of atrophy. The cervix and uterus were usually atrophic. Urine and blood examinations were all negative. In three patients *Trichomonas vaginalis* was found in the vagina.

Treatment consisted of the administration of estrogenic preparations by mouth, by mouth and by intramuscular injection, and by intramuscular injections alone. The preparation used for mouth administration was progynon, and that for intramuscular use, progynon, and theelin in oil. The medication was prescribed three times daily, whereas the injections were given once a week intramuscularly.

Three patients were treated by medication only. The treatment lasted from one to five and one-half months, the average time being two and one-half months. During this period total doses of from 27,000 to 630,000 mouse units were given. The average was 360,400 units. Six patients were treated by mouth and intramuscular injections over a period of from ten to twenty-eight months, the average time being fifteen months. During this time 210,000 to 630,000 mouse units were given by mouth and from 4,000 to 120,000 international units were given by injection. The average dosage was 360,500 mouse units by mouth and 33,000 international units by injection.

Sixteen patients were treated by injection alone, over a period of from one to seven months; the average time under treatment was three and one-half months. During the time from 2,000 to 70,000 international units were used. The average dosage was 24,000 international units.

No douches or other treatments were combined with the use of the estrogenic hormones.

The results of treatment were as follows:

METHOD	MOUTH	INJECTION	BOTH
Number of patients	3	16	6
Cured	3	6	2
Improved, symptoms only	–	5	1
Improved, signs only	–	0	0
Improved, both	–	4	3
No improvement	–	1	–
Relapse, 12 patients	1	6	5
Relapse, symptoms only	–	2	–
Relapse, signs only	–	1	–
Relapse, both	1	3	5

The eleven patients who were cured had a complete disappearance of all symptoms as well as a restoration of the mucosa to normal appearance.

All but one of the remaining patients were relieved of the distressing itching, burning, and discharge.

Relapses occurred in twelve patients from one to five times within a week to five weeks after discontinuing treatment. Renewed improvement followed resumption of treatment.

The one patient who failed to show any improvement under treatment had an adhesive vaginitis.

DISCUSSION AND SUMMARY

It has been shown that the estrogenic substances produce a cyclical change in the vaginal mucosa even after the menopause.

From the results of treatment of senile vaginitis with these substances, it is evident that the shedding and reformation of the mucosa eliminates the underlying pathology present in vaginitis. The normal mucosa thus produced is better able to resist those factors, whether of infectious or atrophic character, which cause the vaginitis. In this way a cure is brought about.

Even when a cure is not complete, the relief of symptoms justifies the use of estrogenic substances in the treatment of senile vaginitis.

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151 West 77th Street
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AN ANALYSIS OF 569 FORCEPS OPERATIONS*

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THE data presented in this paper have been compiled exclusively from the private practice of the authors. From January, 1932, to June, 1935, a careful, detailed record has been kept of all forceps operations performed by us, anticipating a time when the number would be sufficiently large to warrant an analysis. The group of cases which we wish to present consists of 569 cephalic presentations, 2 of which were brow, the remainder being vertex.

Number of forceps operations, 569, distributed as follows: High 1, mid 178, and low 390.

The indications were: Prophylactic 358, occiput posterior 121, transverse arrest 42, contracted outlet 21, inertia uteri 19, preeclamptic toxemia 6, and brow presentation 2.

The maternal morbidity among the midforceps (178) was 11 (6.17 per cent), with one death (59 per cent), and low forceps (390) was 29 (7.43 per cent).

The total maternal mortality therefore was 1 (0.18 per cent), and the maternal morbidity, 40 (7.04 per cent).

The number of patients requiring more than two weeks' hospitalization was 6 (1.23 per cent).

The following is a brief description of the fatal case.

White primipara, aged twenty-nine years. Physical examination and pelvic measurements were normal. She was admitted to the hospital in labor and during labor three rectal injections of paraldehyde and benzyl alcohol and three hypodermics of morphine sulphate, gr. ¼ were ordered for the patient. The technic used has been described by one of the authors[1] in a recent publication. The patient was delivered of a living female infant weighing 7 pounds 1 ounce by means of midforceps after manual rotation of a deep transverse arrest and a left mediolateral perineotomy. Eighteen hours after delivery the patient developed marked abdominal distention, which was relieved somewhat by pituitrin and enemas. Three days after delivery it was discovered that the patient had by mistake received a mixture of formaldehyde, paraldehyde, and benzyl alcohol per rectum during her labor. Appropriate antidotes were immediately given, but with little hope, as the action of formaldehyde on mucous membranes is extremely rapid. The patient died on the ninth postpartum day, death being due to (1) extensive ulcerative colitis, (2) generalized serofibrinous peritonitis, and (3) generalized toxemia.

*Read at a meeting of the Washington Gynecological Society, Washington, D. C., October 26, 1935.

As paraldehyde has become widely used in the past few years as an obstetric analgesic, the authors would like at this time to caution those who are employing this drug to be extremely careful as to its source and the method of dispensing. The similarity of names "paraldehyde" and "formaldehyde" offers a potential source of error which must be carefully guarded against.

The mortality and morbidity figures given above represent the total uncorrected results. Obviously the fatal case was not due to the midforceps delivery, but it was an obstetric death and must be classified as such. The morbidity in this series follows the standard suggested by the American College of Surgeons, which demands that a patient should be considered febrile if a temperature of 100.4° F. appears on any two consecutive days, excluding the first. May we add that in this series temperature readings were recorded at 8 A.M., 12 Noon, 4 and 8 P.M. It will be seen that the great majority of the patients in this group were discharged from the hospital within two weeks after delivery, and that six or 1.23 per cent required more than two weeks' hospital care.

Any attempts at giving corrected maternal mortality and morbidity figures are filled with danger. There still exists a great difference of opinion in regard to reporting such figures, and many obstetric clinics have their own standards. The medical profession is looking forward to the time when a uniform method of reporting maternal mortality and morbidity statistics is adopted. Certainly the recent publications of Adair,[2] Stander,[3] Ward, Goff, and Aldridge,[4] and others have shown conclusively that such a uniformity is absolutely necessary if any value is to be placed on any reported statistics. In this series, therefore, no correction has been attempted. Cases of mastitis and infection of the urinary and respiratory tracts are reported simply as febrile.

TABLE I. INFANT MORTALITY

Midforceps (178)			4, or 2.24%
Stillborn with intracranial hemorrhage		1	
Intracranial hemorrhage, death on sixth day		1	
Monster		1	
Macerated		1	
Low Forceps (390)			9, or 2.30%
Stillborn with intracranial hemorrhage		1	
Intracranial hemorrhage		2	
Death on second day	1		
Death on fourth day	1		
Prematurity		3	
Monster		1	
Macerated		2	
Total Infant Mortality			13, or 2.28%

The infant mortality given above represents the total uncorrected results. We believe in what Stander[3] has recommended, "that fetal mortality rates should be reported as total infant mortality by which is meant all babies weighing 1,500 gm. or over, or measuring 35 cm.

or more, born dead or dying within fourteen days of birth, and that such mortality rate be reported in an absolutely uncorrected form."

It seems desirable at this time to give a résumé of the methods practiced by the authors as regards the intrapartum care of the patients, reported in this series. But even before this résumé, let it be borne constantly in mind that all of these patients were private patients, they received adequate antenatal care, and entered the hospital in good physical condition. Proper and intelligent antenatal care certainly reduces the incidence of complications during the intra- and postpartum periods.

Practically all of the patients received one of two types of obstetric analgesia. In approximately one-third of the cases the Gwathmey method was employed, while the remaining two-thirds of the patients were given paraldehyde and benzyl alcohol according to the method recently described by one of the authors.[1] For the actual forceps delivery ethylene was used in the great majority of cases. When it was impossible to secure the services of an experienced anesthetist, ether was administered. The average length of labor for all types of cases as shown in Table II is certainly shorter than most generally accepted figures.

TABLE II. MISCELLANEOUS

	LOW FORCEPS		MIDFORCEPS	
	PRIMIPARAS	MULTIPARAS	PRIMIPARAS	MULTIPARAS
1. Number	183	207	121	57
2. Perineotomies	183	176	121	52
3. Average length of labor	14′23″	10′16″	18′48″	12′54″
4. Average number vaginal examinations	2.42	2.07	3.83	2.83

Vaginal examinations, with proper preparation of both the patient and the doctor, were performed at any time when an intelligent interpretation of the progress of labor was desired. The average number of vaginal examinations for all types of cases may be seen in Table II. Recalling that the total uncorrected maternal morbidity in this series is 7.04 per cent, it is our belief that vaginal examinations carefully performed in a proper environment entail no added risk to the patient.

When occipitoposterior positions are encountered, it is our custom to rotate manually and deliver by forceps if progress ceases for one hour, the head being in the pelvis and the cervix fully dilated.

The recent works of Caldwell, Moloy and D'Esopo[5] upon the structure of the female pelvis and the effect of its variations upon the course of labor lead one to believe that in some instances the pelvis is best adapted to the passage of a head in the posterior position. Some operators accomplish rotation by means of forceps, after the method of Bill, or with the Kielland instrument. In this series it has seemed best to rotate in all cases and to rotate with the hand.

We deliver by low or outlet forceps all heads which reach the perineum, and we perform perineotomies whenever a perineum is present.

CONCLUSIONS

1. The use of forceps need not add to obstetric morbidity or mortality, maternal or fetal.

2. Only through the publishing of uncorrected statistics by all authors may comparable reports be obtained.

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1835 Eye Street, N. W.

ADENOCARCINOMA OF SUPERNUMERARY BREASTS OF THE LABIA MAJORA IN A CASE OF EPIDERMOID CARCINOMA OF THE VULVA*

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BREAST tissue in the labia is rare. Adenocarcinoma of breast tissue of the labia has not been reported. The presence of epidermoid carcinoma in the same area makes this case an outstanding one, since two types of cancer are found in the same individual.

Of the many cases of aberrant breast tissue reported, only seven have been reported involving the labia. Hartung[1] in Germany in 1872 reported the first case in a young girl who presented herself with a small pedunculated mass attached to one of the labia and secreting a milky fluid. This tissue was removed and found to be breast tissue. DeBlasio[2] in Italy in 1905 reported a case where a young girl had nipples on each labium, and at puberty large masses developed into breast tissue, which became larger with each pregnancy. Bell[3] in 1926 reported a case that came to him following an accident to the vulva. A swelling occurred and it was thought to be a boil because it was always discharging milky fluid. Its removal proved to be breast tissue. Three years later the patient came back with extensive epidermoid carcinoma of the vulva. Purvis[4] in England in 1927 reported a case where the patient had her breasts removed in early adolescence. Later on when she became pregnant she developed masses in the labia. The removal proved them to be breast tissue. McFarland[5] in 1931 reported a case of mammary gland of the labia proved by section. Fridel[6] in Germany in 1932 reported a case of aberrant breast tissue in the right labium which had undergone changes to fibroadenoma. A recent case is one reported by Mengert[7] in June, 1935. A small tumor was discovered during a routine prenatal examination. Following delivery and with the arrival of the milk, this mass became larger, and removal proved it to be breast tissue.

*Presented at a meeting of the Brooklyn Gynecological Society, October 4, 1935.

The etiology of supernumerary breasts or aberrant breast tissue is best explained by the darwinian theory of the "Descent of Man." It is an atavistic expression of our ancestorial history or a reversion to lower animals. In whales, dolphins and lemurs we find the normal breasts at the vulva. Experience shows that the aberrant breast tissue is usually found along the primitive milk line, which is detected in 10 mm. embryos, from axilla to groin.

The presence of adenocarcinoma of aberrant breast tissue is not uncommon in the axilla or on the pectoral surfaces; however, no case has been reported of adenocarcinoma of aberrant breast tissue in the labia. Bell's case developed squamous cell carcinoma of the vulva three years after extirpation of the breast tissue. Fridel's patient presented herself with a fibroadenoma.

Mrs. F. R. (Hospital No. 27751), negress, forty-nine years of age, nullipara, was admitted to the Gynecological Service of our Hospital on July 24, 1935. She com-

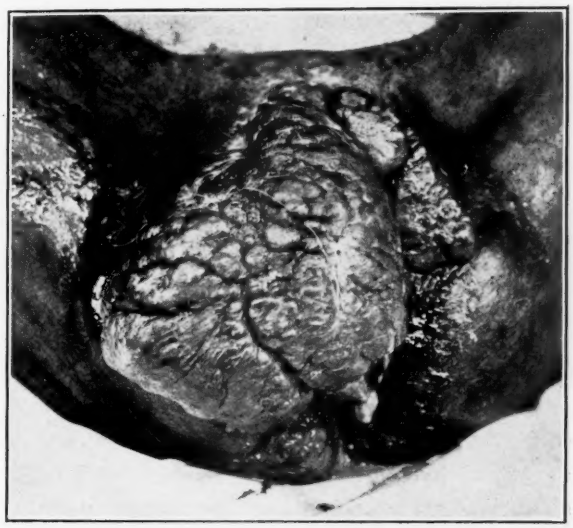

Fig. 1.—General view of vulvar tumor containing breast tissue.

plained of vaginal bleeding and discharge. She was completely disoriented and her history was unreliable. From one of her relatives it was gleaned that she had been suffering from a growth in her vagina for one year. Physical examination revealed an emaciated and cachectic negress in the final stages of carcinomatosis. There was a hard and large inguinal adenopathy. In the region of the vulva there was a large mass (Fig. 1) 8 inches long and 6 inches wide at the base and originating in the vicinity of the right labia. On the opposite side there were numerous smaller masses extending for the entire length of the left labia. Upon separating the masses there were extensive areas of ulceration and sloughing. The vaginal canal or its remains was indurated and hardly the tip of the finger could be introduced. The rectovaginal septum was completely sloughed and the edges were thick and ulcerating. She was incontinent of feces and urine. Wassermann report was negative.

Clinical Diagnosis.—Carcinoma of vulva.

There were two biopsies taken, one from the mass on the right and another from the region of the junction of the mass with the vagina. The hospital pathologist, Dr. Hala, reported the following: "Sections show fibroblastic tissue in which there

is present a newgrowth extremely disorderly in architecture. Primarily it is adenomatous, but in some areas it shows scirrhous type of growth. The neoplasm is malignant'' (Fig. 2).

Biopsy Diagnosis.—Adenocarcinoma of breast tissue. Some normal islands of breast tissue. ''Section shows a newgrowth which is of epidermoid type; there are numer-

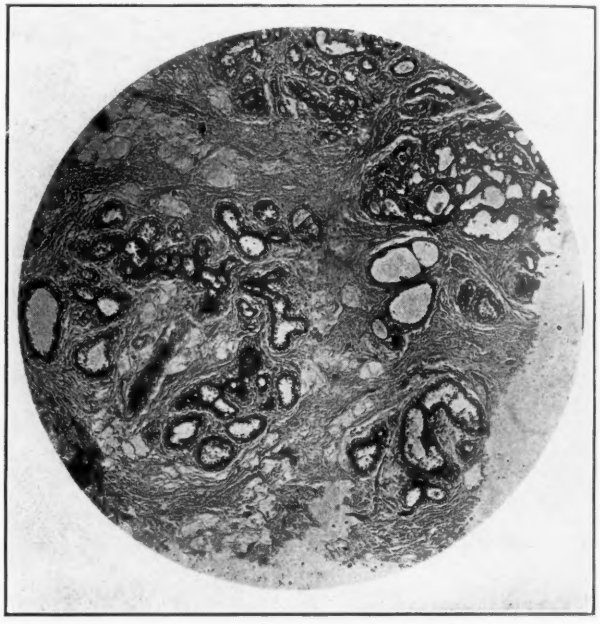

Fig. 2.—Section from tumor on right labia, showing malignant changes in the acini of breast tissue.

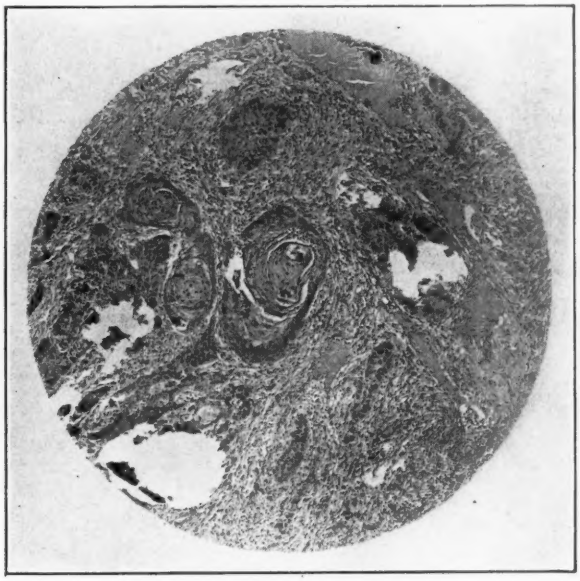

Fig. 3.—Section from remaining rectovaginal septum, showing epidermoid type of new-growth and pearl formation.

ous small and large islands of neoplastic tissue infiltrating into the underlying subcutis a tendency to pearl formation and to keratinization are well marked" (Fig. 3).

Final Diagnosis.—Epidermoid carcinoma of vulva. Our patient died on Aug. 14, 1935, of carcinomatosis. No necropsy was obtainable.

Comment.—This case presents two types of carcinoma, the adenocarcinoma extremely rare, in aberrant breast tissue of the labia and the epidermoid carcinoma of the vulva. Perhaps the same irritating force that produced the vulva cancer was responsible for the carcinoma developing in the breast tissue.

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855 Ocean Avenue

OBSERVATIONS ON THE USE OF COLLIP'S EMMENIN IN THE MENOPAUSE*

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(From the Department of Gynecology, Woman's Medical College of Pennsylvania)

THE relief of the vasomotor symptoms of the menopause by means of endocrine substances has been an object of therapeutic endeavor since the introduction of the popular, but probably ineffective, "lutein tablets" of Fränkl in 1898.

Among recent additions to this list of substances is an estrogenic extract obtained from human placentas by Collip,[1] of Toronto, in 1930. This substance produces estrin in young animals but not in mature castrates. Collip called it "emmenin." He states that "it probably acts through stimulation of the intact ovary," and "we cannot expect relief from menopausal symptoms after panhysterectomy."

Collip[2] treated eighteen menopausal patients with emmenin. Fourteen of these women were relieved. "No relief was obtained in cases of long standing or in castrates. Cases of recent origin, less than one year after the last menstruation, gave the best results."

I have given this extract a trial, using Emmenin liquid (complex type). This is said to contain "the hormone emmenin, associated with ether-soluble placental principles."

The liquid was given by mouth, one teaspoonful in water three times a day, to eighteen women whose periods had ceased from six weeks to eighteen years. In eight of these women the menopause was physiologic. In seven of them, it was surgical (after bilateral salpingo-oophorectomy with or without supravaginal hysterectomy). In three women, the menopause had been produced by the intrauterine application of radium.

*Presented at a meeting of the Obstetrical Society of Philadelphia, October 3, 1935.

One patient, fifty years of age, was completely relieved of incapacitating headaches, hot flashes, etc., which developed fourteen years after a supravaginal hysterectomy in the course of which the ovaries were preserved. This patient and one of the radium patients strengthen the belief that a secondary physiologic menopause occurs at the normal age in women whose ovaries were conserved in the course of

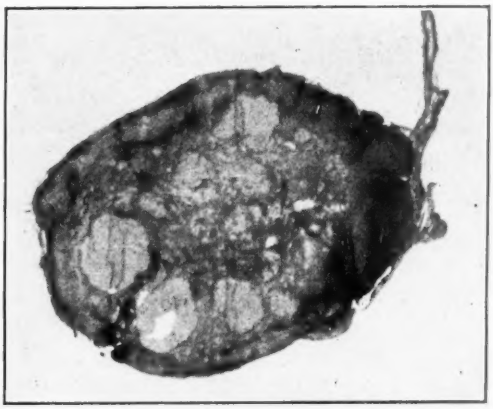

Fig. 1.—Section of ovary from woman sixty-two years old. ×6.

Fig. 2.—Section of ovary from woman sixty-two years old. ×25.

a hysterectomy performed at a relatively early age and also in women whose ovaries were irradiated by radium or x-ray at a relatively early age.

Ten of the eighteen women treated believe their vasomotor disturbances were improved by the use of emmenin. Eight of the ten were very positive in their statements; two were rather unconvincing. The eight positive results may be summarized as follows:

PHYSIOLOGIC MENOPAUSE

CASE 1.—A. S., aged fifty. Periods irregular for one year. Last period March, 1935. In July, 1935, she came complaining of hot flashes, dizziness, nausea, and insomnia. Emmenin was prescribed, teaspoonful three times a day. Symptoms were definitely relieved. In September, 1935, patient reported symptoms much less severe; takes emmenin intermittently; "would not be without it."

CASE 2.—E. A., aged forty-two. Her periods ceased abruptly July, 1934. In January, 1935, she complained of frequent, severe hot flashes, insomnia, headache, and depression. Blood pressure 160/80. Emmenin was prescribed. On January 25, she reported marked relief of symptoms. Blood pressure 128/70. In May, 1935, patient came again on account of the same symptoms, having discontinued emmenin for two months. After resuming its use, she again reported prompt relief.

CASE 3.—H. M., aged forty-two. Periods were scanty and infrequent for six months. Last period March 10, 1935. June 2, 1935, she complained of dizziness and hot flashes followed by drenching prespiration. Emmenin was prescribed with prompt relief of symptoms.

MENOPAUSE AFTER BILATERAL SALPINGO-OOPHORECTOMY AND HYSTERECTOMY

CASE 1.—M. S., aged forty-nine. On Dec. 17, 1934, supravaginal hysterectomy and bilateral salpingo-oophorectomy. On April 8, 1935, she complained of severe hot flashes, headache, insomnia, and nervousness. Blood pressure 150/80. Emmenin was prescribed. After one month, patient reported no headaches, no hot flashes, and no insomnia. In September, 1935, she reported symptoms much less severe; takes emmenin occasionally; positive it helps her.

CASE 2.—D. M., aged forty-three. On May 3, 1934, supravaginal hysterectomy and bilateral salpingo-oophorectomy on account of pressure producing myoma with adherent appendages. In December, 1934, she complained of severe hot flashes which were not relieved by theelol. Emmenin was prescribed with definite improvement.

RADIUM MENOPAUSE

CASE 1.—A. R., aged forty-three. On March 3, 1935, she received intrauterine application of radium (2,400 mg. hr.) on account of dysfunctional bleeding. On April 24, 1935, patient complained of hot flashes, dizziness, headache, and nervousness. Blood pressure 140/70. Emmenin was prescribed with marked relief of symptoms.

SECONDARY PHYSIOLOGIC MENOPAUSE

CASE 1.—F. G., aged fifty. In 1921 a bleeding myoma of the uterus was removed by supravaginal hysterectomy; the ovaries were not removed. In 1935, patient complained bitterly of hot flashes, headache, dizziness, depression, confusion, and exhaustion; blood pressure 180. Emmenin prescribed with amazing relief of symptoms.

CASE 2.—E. R., aged fifty-three. On Oct. 10, 1932, intrauterine application of radium (6,000 mg. hr.) on account of beginning carcinoma reported in tissue removed in the course of a cervical repair. Cessation of periods was followed by vasomotor disturbances which continued for about a year and a half. After one year's freedom from symptoms, they returned in February, 1935. Emmenin was prescribed with marked relief. In September, 1935, patient was positive that emmenin helped her.

SUMMARY

1. Emmenin liquid (complex type) was given to eighteen women complaining of the vasomotor disturbances of the menopause.

2. Ten of these women were improved; eight very definitely, two rather indefinitely.

3. In the eight patients definitely improved, treatment was instituted soon after the onset of symptoms (from one to seven months). In two of them, the menopause was surgical, following supravaginal hysterectomy and bilateral salpingo-oophorectomy.

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DISCUSSION

DR. WINIFRED B. STEWART.—My views are in accord with those of Dr. Macfarlane. My experience, however, has been chiefly with the abnormal mental manifestations of this period, which, as is well known, vary greatly in both severity and duration. Irritability, nervousness, and mild depression are very common. Anxiety states, emotionalism, feelings of inadequacy and acute depressions attended by suicidal tendencies also occur, and delusional states, particularly those of infidelity, are frequently encountered. These psychoneurotic and psychotic states of middle life are no longer thought to be a distinct clinical entity. As in other periods of life, the personality type of the individual determines the type of psychosis.

Insanity is a state of mental decompensation which may be caused by any one of a number of endogenous or exogenous factors. The psychoses of the menopause are probably a result of the endocrine imbalance which occurs at this period and therefore the use of suitable endocrine substances is believed by many investigators to be the rational form of treatment. Recent advances in endocrinology have contributed products which seem to be far more efficacious for this purpose than the extracts formerly at our disposal. Within the past two years, Severinghouse reported good results with folliculin in the treatment of mental symptoms of the menopause and Werner and associates used theelin with encouraging results in a large series of involutional psychoses in Missouri City and Missouri State Hospitals.

I have employed emmenin in the treatment of five cases, four of which were definitely improved. However, none of these four was committably insane. Three were treated relatively soon after the onset of symptoms. One patient, treated eight years after a bilateral oophorectomy, theoretically should not have been benefited, but showed definite improvement.

While these results are very encouraging, in order properly to evaluate the relative efficacy of this form of treatment, it will be necessary to study a larger series of cases, preferably under institutional supervision.

MASSIVE COLLAPSE OF THE LUNG COMPLICATING PARTURITION

HARRISON BETTS WILSON, M.D., HACKENSACK, N. J.

SIR JOHN ROSE BRADFORD defines massive collapse of the lung as "an unusual condition in which the lung without the pressure of any gross lesion such as bronchial obstruction, pleural effusion, etc., interfering with the free entry of air, causes airlessness to a great or less degree."

Up to the present time four principal theories or hypotheses have been set forth as possible explanations of massive collapse of the lung.

1. Pasteur[1] advanced the theory that the collapse of the lung was due to pressure exerted by the collapsed chest wall and elevated diaphragm which resulted from paralysis of these structures. Under this condition respiration became sluggish, and permitted the collection of secretions in the bronchioles which caused this obstruction, and the air remaining in the alveoli of the obstructed area was absorbed by the circulating blood. Therefore he places pressure of the chest wall and diaphragm as primary, and the lung collapse as secondary causes.

2. Briscoe[2] states that "due to the onset of inflammation affecting the muscles of the crus situated behind the peritoneum, one-half of the diaphragm and its synergistic and antagonistic muscles are out of action owing to the inflammation of the muscle or the pleural membrane covering it." The resultant respiratory disturbance leads to collapse.

3. Jackson and Lee[3] contend that "obstruction of the bronchioles by secretions is the entire explanation, such a condition being all that is necessary for all the other factors of the condition, any disturbance of the respiratory function being incidental."

4. Bradford[6] advances the explanation that "some spasmodic reflex of the bronchioles causes them to become occluded, thereby permitting future absorption of air in the segment of the lung involved."

Sante[4] summarized the hypotheses of this condition by saying "the cause is not known, but it seems most probable that some infection or insult to the region of vagus supply produces a reflex action on the bronchioles permitting their temporary collapse. Once approximated, the walls of these bronchioles are held in apposition by cohesion, collapse of the lung following, owing to the absorption of alveolar air by the circulating blood. Relief of the obstruction results in the sudden re-inflation of the lung."

Potter[5] states that "the treatment is first postural, the patient being turned on his side with the involved lung uppermost and induced to cough. This treatment will cause the lung to re-inflate and the symptoms to subside. If the case is of short duration, the lung clears very rapidly, but in cases that have existed a few days there may be some delay due to an accumulation of mucus which is Nature's method of producing cough and finally recovery. These cases may have an abundant mucous expectoration. If postural treatment does not re-inflate the lung, bronchoscopy is indicated." This procedure is not generally known or appreciated by the profession.

OCCURRENCE

The cases reported thus far in the literature have either followed from some distinct condition such as diphtheria, poliomyelitis, streptococcus septicemia, or some insult to the nervous supply of the vagus, abdominal or chest injuries or operations.

Any of the above described conditions could serve as a necessary reflex stimulus to the constrictor fibers of the bronchioles. None of the available literature reports this condition as a complication of parturition. One such case was observed in the Hackensack Hospital in 1932. Radiographic studies confirmed the complication in this case.

Personal communications from leading obstetricians in the United States failed to disclose any experience in this field.

CASE REPORT

This patient (Case No. 28395), a negress aged twenty-one years, was admitted to the Hackensack Hospital, 11:30 P.M., March 25, 1932, having irregular uterine contractions every fifteen to twenty minutes. She was first seen in the Out-Patient Department of the hospital, Jan. 20, 1932. Her medical and physical history are essentially negative. Present pregnancy, which was her first, showed no abnormality except occasional attacks of nausea in the morning which persisted throughout her

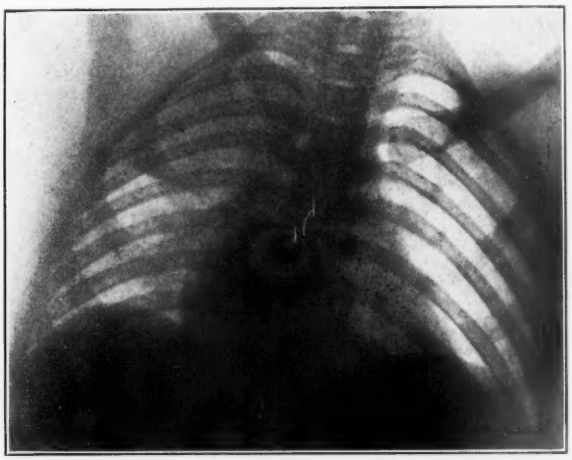

Fig. 1.—First examination, thirty-two hours after delivery. Considerable diminution of illumination of upper lobe and moderate diminution of illumination of middle and lower lobes of right lung, lung markings faintly visualized, narrowing of right chest, and moderate retraction of heart to right. Compensatory emphysema of left lung.

pregnancy, and she complained some of slight swelling of the feet during the last month. Her last menstruation was June 15, 1931; date of expected confinement, March 22, 1932. Physical examination revealed a well-developed and well-nourished female. The tonsils were slightly hypertrophied. The chest was normal, there was a faint systolic murmur at the apex of the heart. The rate and rhythm of the pulse were normal. The pelvic measurements were adequate. Wassermann, urine, vaginal and urethral smears were negative. The blood pressure varied from 100/60 to 118/60. She gained approximately twenty pounds in weight during her pregnancy. About three weeks before confinement the patient had an attack of acute bronchitis which had cleared up by the time she was admitted to the hospital. Her labor lasted thirty-eight hours, during which time she had three rests with morphine, ¼ of a grain each, at intervals of about eight hours. The last dose of morphine was given about six hours before delivery. The cervix was completely dilated about eight hours before the patient was delivered. A persistent left occipitoposterior position was diagnosed. The membranes were intact. It was deemed advisable to deliver this patient in view of the fact that she had been in labor thirty-eight hours

and was having good strong contractions with no evidence of rotation. The membranes were ruptured and an attempt was made to rotate the head with Tucker-McLane forceps. This maneuver was unsuccessful and version and extraction were then done under ether anesthesia with a small midline episiotomy. There was no postpartum hemorrhage and the patient left the delivery room in good condition. Approximately two and one-half hours later she began to cough and became very

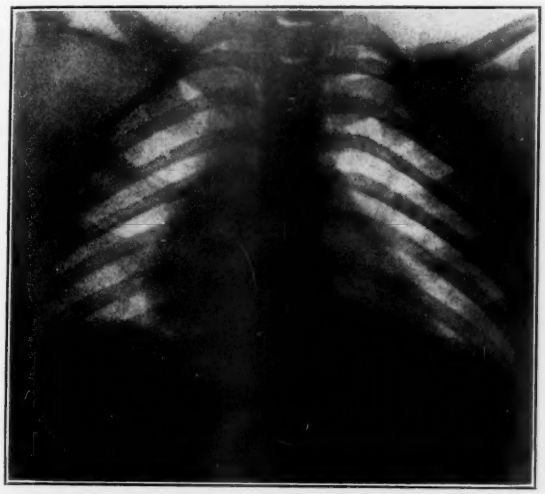

Fig. 2.—Second examination, four days after delivery. Moderate incomplete massive atelectasis of right lung, and moderate retraction of heart to right.

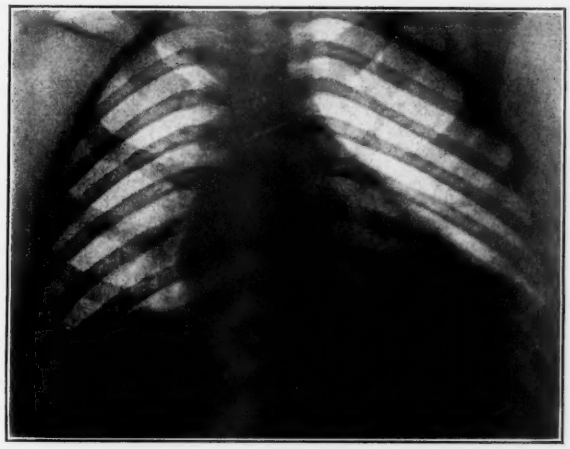

Fig. 3.—Third examination, five days after delivery. Complete recovery.

apprehensive. Her respirations increased to thirty-six per minute and the pulse rate to 140. She complained of pain in the right side of her chest. At this time she was raising purulent sputum streaked with blood. Our first thought was that the patient was developing pneumonia. We ordered supportive treatment and an x-ray of the chest. Auscultation elicited coarse râles over the entire right side, loudest toward the median line. On March 28, an x-ray showed a massive atelectatic collapse of the right lung. March 31, another x-ray showed the collapse of the lung

with evidence of beginning reinflation. April 1, x-ray showed a complete reinflation of the collapsed lung.

Sputum examination showed many pus cells and a few streptococci. Blood count revealed four million red cells and a normal leucocyte count. The urine was negative. This patient was discharged from the hospital April 7, 1932, apparently well. The massive collapse of the lung was the only complication in her postpartum period and she is at the present time in good health.

The temperature curve, with no elevation over 101.8° and that at the time of delivery, showed conclusively that there was no pneumonic infection present.

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PREGNANCY IN SPORADIC CRETINISM

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PREGNANCY in the sporadic cretin is rare if judged by the paucity of reported cases found in a fairly extensive review of the indexed literature.

B. A., aged twenty, was admitted to the University Hospital Jan. 20, 1933, on the Medical Service. She had been born of normal parents and reared in Saginaw, Michigan, with ten normal siblings. Past history revealed physical and mental retardation, tinnitus, diminished auditory acuity, marked sensitivity to cold, hypokinesis, dysmenorrhea, and menorrhagia. The menses had been irregular since onset at the age of fourteen. Typical cretinoid characteristics were found on physical and roentgenologic examinations. The patient was 135 cm. (53½ inches) in height and had a basal metabolic rate of minus 25 per cent. Diagnoses of sporadic cretinism and bilateral nerve deafness were made.

Desiccated thyroid gland was administered daily. The patient left the hospital after two months but returned for monthly examinations over a period of a year and was subsequently seen by her local physician. Thyroid medication, over this period, varied from 0.032 gm. to 0.8 gm. (½ to 12 gr.) daily. Antuitrin was administered by her local physician during May and June, 1934 (1 ampule daily for two weeks, and on alternate days for two weeks). The basal metabolic rate vacillated with the amount of thyroid therapy reaching a high of plus 9 on one occasion and falling to minus 26 per cent after a period of discontinuance of the drug. Symptomatic improvement, including relief from deafness, was noted when the rate approached normal.

This patient was readmitted Jan. 11, 1935, to the obstetric service. She had added two inches to her height in two years. Libido had evidently been stimulated, there having been no heterosexual interest or intercourse prior to 1934. Her last menstrual period began July 25, 1934. No desiccated thyroid was taken after the following October. She was judged to be six or seven months pregnant. The fetal skeleton was normal by roentgenography.

During the last trimester the basal metabolic rate rose from minus 9, eight weeks before delivery, to plus 7 per cent in the final week (Fig. 1). Blood cholesterol content was 370 mg. per cent (Fig. 1). The intelligence quotient was 63. Pheno-

sulphonephthalein and urea clearance tests were within normal limits, although, in the immediate antepartum period, the patient developed a mild toxemia of pregnancy which was controlled by bed rest.

April 19, 1935, she delivered spontaneously after a six-hour labor. A male child weighing 3,060 gm. (7 pounds and 12 ounces) was born without mishap other than moderate postpartum hemorrhage. Without thyroid medication the patient's basal metabolic rate dropped to minus 18 per cent within two weeks. Blood cholesterol* fell to 210 mg. per cent, having been 360 mg. per cent during labor. However, this value rose to 243 before desiccated thyroid was resumed during the third postpartum week.

The infant was apparently normal by physical and roentgenologic examinations. No thyroid gland was palpable. The infant was fed an evaporated milk formula without breast milk and gained 300 gm. in three weeks.

Cord blood contained 146 mg. per cent cholesterol as compared to the high value found in the mother's blood during labor. The infant's plasma cholesterol was present in 137 mg. per cent on the third day, 113 on the sixth, and 103 on the twelfth day. Cord blood contained creatinine in 1.5 mg. per cent.† On the sixth day the total twenty-four-hour urinary excretion of creatine was 16 mg., with 24 mg. of pre-

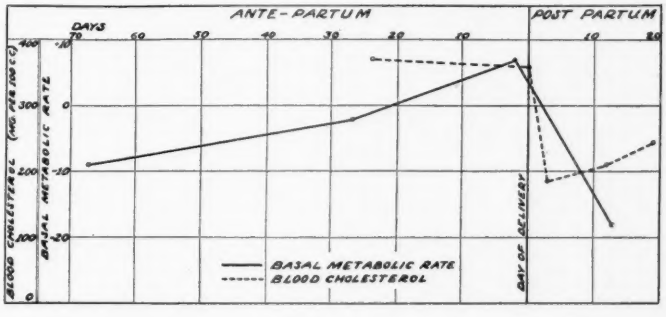

Fig. 1.

formed creatinine. On the twelfth day there were 33 mg. of creatine and 64 mg. of preformed creatinine. The creatinine coefficients for the sixth and twelfth days were 12.9 and 31.2, respectively.

CONCLUSIONS

The cholesterol content of the cord blood and that during the first week were higher than the normals found by Gordon and Cohn,[1] but, thereafter, the values fell to average figures. If creatine excretion can be used as an index of an infant's metabolic rate, as suggested by Poncher and others,[2] it may be inferred that the metabolism of this infant was sluggish immediately after birth but rose during the investigative period. This inference is borne out by the decrease in cholesterol which would seem to indicate increased metabolism.[3] Apparatus was not then available for calorimetric studies.

The evidence at hand leads us to believe that an essentially normal individual was born of a sporadic cretin mother whose own metabolic rate had been maintained at a satisfactory level during most of her pregnancy without medication. Congenital thyroid enlargement, as has been found in animals born of thyroidectomized mothers,[4] has been anticipated but not found in a case similar to ours.[5] An elevation of

*Cholesterol values were obtained by the Sackett modification of the Bloor method.

†The methods of Folin were used for determinations of blood creatinine and urine creatine and creatinine.

metabolic rate and cholesterol occurs in pregnancy,[6] but whether this is due to factors endogenous to the mother's own body or to factors supplemented by the fetus cannot definitely be stated.

Desiccated thyroid gland and antuitrin medication previous to conception suggest the alleged thyroid-pituitary relation to sexual function.[7]

The present report of another case of pregnancy in sporadic cretinism and delivery of an apparently normal infant is added to the literature.

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A NORMAL HUMAN OVUM IN A STAGE PRECEDING THE PRIMITIVE STREAK*

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THIS embryo was found in a uterus removed because of fibromyomas. There was also a dermoid cyst of the right ovary. The blastocyst, embedded in the endometrium of the posterior wall, was fixed with the surrounding decidua and adjacent myometrium in formol-Zenker's solution within nine minutes after the uterine blood vessels were clamped. The entire blastocyst was cut serially.

The patient, aged thirty-eight, had had three normal full-term deliveries, the last in June, 1934. Her menstrual periods began at thirteen years of age, occurred regularly every twenty-eight days, the flow lasting four to five days. The last menstrual period began Feb. 15, 1935 and ended Feb. 19, 1935. The period expected on March 15, 1935 failed to appear. The abdominal supracervical hysterectomy was done on March 20, 1935, thirty-three days after the last menstrual period. An accurate coital history could not be obtained.

The age of this embryo is estimated to be about fifteen days and is slightly younger than the Peter's ovum.

The measurements made on the slides and on the model at 250 diameters are as follows:

External chorion (including full extent of the trophoblast)	$3 \times 3.0 \times 1.9$ mm.
Internal chorion	$2.13 \times 1.71 \times 1.01$ mm.
Amnion	$0.224 \times 0.186 \times 0.167$ mm.
Yolk sac	$0.197 \times 0.160 \times 0.120$ mm.
Embryonic disc	0.184×0.188 mm.
Greatest length of mesodermal villus	0.27 mm.

*Aided by a grant from the Rockefeller Foundation to the University of Chicago.
Note: A detailed description of this ovum will be published later.
Read at a meeting of the Chicago Gynecological Society, October 18, 1935.

The blastocyst situated superficially in the endometrium is surrounded by a few short mesodermal villi. There is a little degeneration of the tissues where the fetal and maternal portions join. The walls of a few venous spaces have been penetrated and in some places replaced by fetal trophoblast. At the point of entrance of the ovum is an adherent organized blood clot. Beneath the ovum are large venous spaces and several endometrial glands distended with blood. The uterus was not touched or traumatized during the process of obtaining and fixing the specimen.

The embryonic anlage is attached at the deepest pole of the chorion by a short body stalk. There are no blood vessel formations in the stalk.

The amnion in cross-section is triangular with the peak embedded in the stalk. At the apex of the triangle the cells of the amnion are cuboidal and in several layers in contrast with the thin, elongated cells of the lateral walls. At the junction with the embryonic disc there is an abrupt change from one to the other.

The embryonic disc is almost flat except for a slight upward curve at the lateral, cephalic, and caudal edges. The cells are two or three layers deep in places. The ventral surface of the disc is distinctly separated from the entoderm by a sharp basement membrane. There is no mesoblastic tissue between the disc and the yolk sac.

The yolk sac is smaller than the amnion. Beneath the disc, the entodermal cells are cuboidal and are arranged in a single row. The other cells of the yolk sac are thin and elongated. There is no formation of blood vessels in the wall.

104 South Michigan Avenue

DISCUSSION

DR. J. P. GREENHILL.—The fact that five ova less than twenty days of age are reported by one group of workers is astounding. In the entire world literature there are less than 75 ova as young as this.

Dr. Fitzgerald said that the menstrual ages of the two cases reported in detail was identical and yet one ovum was nineteen days old whereas the other was only fourteen days of age. All authors including myself, who have reported studies of young ova have specified the age of the ovum in days. However, undoubtedly in the future we shall have to revise the ages of ova already reported. The reason for this is that there are too many unknown factors in the process of ovulation, fertilization, and growth. For example, we do not know in the human being the exact day of ovulation, the exact time of fertilization, and the time it requires for a fertilized ovum to traverse the fallopian tube to reach the uterine cavity. We are not certain of the exact duration of time human ova and sperm are capable of fertilization although we are almost sure the period of time is a matter of hours. We do not know when a fertilized ovum is ripe enough for implantation in the endometrium nor at what stage in the development of the endometrium an ovum is capable of being received. Furthermore, in some instances at least, clinical data concerning the dates of coitus and menstruation are not accurate. There is no unity of opinion concerning which structures of the ovum should be used as the criterion for the determination of the age of an ovum. Some authorities believe it should be the trophoblast whereas others consider the stage of development of the embryo a more reliable index. Again not all ova of the same stage of growth are necessarily of the same age. There may be differences in the rate of growth in young ova just as there are variations late in intrauterine life and in extrauterine existence.

DR. HAROLD O. JONES.—If tissue is to be of any value for accurate study, it should be fixed and examined at once, which means that we should organize our

ideas about availability of tissues before operating procedures are carried out. We always try to arrange it so that one of us will be about when another one is operating. Thus the tissue removed is fixed. Ideally it would be better if microscopic observations were made as soon as the tissue is removed.

DR. BREWER (closing).—Dr. Greenhill said that probably there are less than 75 ova under twenty days of age reported in the literature. There are really less than 50. We determined the ages of our ova from our own statistics since we have accurate coital history in two of the five cases.

DR. GEORGE W. BARTELMEZ.—It is a great compliment to this Society to have in it a group of men so vitally interested in embryology. Studies of this kind will throw light on fundamental biologic problems such as the variability in the time of ovulation and the viability of the egg.

SPONTANEOUS DELIVERY COMPLICATED BY RECTAL STRICTURE, RECTOVAGINAL FISTULA AND RUPTURE OF THE RECTUM

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RUPTURE of the rectum during delivery has not been recorded in the literature. Rectal stricture and rectovaginal fistula complicating pregnancy and labor are uncommon but have been noted frequently. In the obstetrical service of The Harlem Hospital, rectal stricture as a complication of labor was found once in 1,500 cases. The occurrence of two catastrophic events served to focus attention upon a relatively rare condition and to cause the preparation of this report. In a period of several months, two deaths occurred on the service in cases complicated by rectal stricture and rectovaginal fistula. One of these was an operative delivery. The second case was terminated spontaneously after a short, rapid labor. Consent for necropsy was obtained in this second case and the clinical and relevant necropsy findings are here recorded.

Mrs. H. P., aged thirty-two years, colored, housewife, was admitted to the obstetrical service at 9:30 P.M., on June 24, 1934. She had been cared for during the prenatal period by the out-patient service. The entire prenatal record was negative with the exception of a flat rachitic pelvis. The Wassermann was negative.

She had had two previous pregnancies. The first had terminated in a spontaneous, premature labor in 1926. The puerperium was uneventful and she left the hospital seven days postpartum at her own risk. In July of 1929, she was admitted in active labor which terminated in spontaneous delivery. In the course of this second hospital stay the Wassermann was found to be 4-plus and the presence of a rectal stricture was noted.

With the termination of the puerperium she was referred to the out-patient department for antisyphilitic therapy and treatment for the rectal stricture. This was continued for one year and at the end of that time the Wassermann was negative.

In June of 1930, hospitalization for treatment of the rectal stricture was advised and refused.

On admission on June 24, 1934, the patient was in active labor. A small fetus presented as L.O.A. The fetal heart was audible in the left lower quadrant, regular in rate and rhythm. Rectal examination revealed the presence of a stricture about one inch from the anal orifice. It was firm and inelastic and did not admit the examining finger. Feces were seen emerging from the vagina. General physical examination was negative save for a systolic murmur heard over the precordium. The urine was negative and the blood pressure was 116/70.

Because of the rectal stricture and the contamination of the birth canal by feces, labor was permitted to proceed without further examination. The vulva and perineum were repeatedly flushed and cleansed and three hours after admission the patient delivered spontaneously a male infant weighing five pounds and eleven ounces. The perineum was intact. The placenta and membranes were expressed after separation. Blood loss was estimated at 150 c.c. The general condition immediately following delivery was good. The patient was returned to her bed on the ward one hour later.

Seven hours following delivery, the patient was found in a state of profound collapse, anxious facies and covered with perspiration. The pulse was small, thready, and 160. Blood pressure was 86/40. The abdomen was markedly distended and, through a huge diastasis the distended gut was percussed. The recti to each side were rigid. There was moderate lochia but no free vaginal bleeding.

Immediate efforts were made to combat shock with morphine, intravenous infusion of glucose and saline, external heat and the Trendelenberg position with some improvement in the next two hours. At the end of that time, the pulse again became thready and small and the blood pressure dropped farther. In the presence of this persistent shock and the extreme abdominal distension, surgical consultation was requested. It was the opinion of the consultant that rupture of the sigmoid or rectum above the point of stricture was probable.

With collapse persisting, operative intervention was held untenable. A transfusion of 500 c.c. of citrated blood was performed in a further attempt to relieve shock.

Despite all efforts, collapse persisted and deepened and, sixteen hours following delivery, death supervened.

Relevant Necropsy Findings (Dr. E. Holder, Resident Pathologist).—The general peritoneal cavity contained from 1,500 to 2,000 c.c. of "pea soup like" fluid mixed with fecal matter and having a marked fecal odor. The stomach and small intestines were distended. The omentum was rolled up on itself and was adherent to loops of small gut. All the abdominal viscera were covered by a grayish purulent exudate.

The uterus was lifted from the pelvis. Upon sponging the culdesac clean and exposing the anterior rectal wall, an opening in the rectum was seen, 1.5 to 2 cm. in diameter, which freely communicated with the general peritoneal cavity. There were no adhesions or exudates about the rectal opening.

The bladder mucosa was thin and there was marked congestion of the superficial vessels.

The vaginal mucosa was hemorrhagic; 1.5 cm. from the vaginal orifice an opening 0.5 cm. in diameter was seen, and a probe passed into it emerged at a similar opening in the rectum.

The lower uterine segment was elongated and the vessels were congested. The endometrium was dark and hemorrhagic.

The rectal mucosa was dull gray, 2 cm. from the anal orifice there was an opening which connected with the vaginal opening aforementioned. There was a constriction of the lumen 4.5 cm. from the anal orifice due to dense infiltration of the rectal wall. It was impossible to pass the finger through this constriction. The

rectal induration in the region of the constricted area extended for a distance of 2 to 3 cm. Just proximal to the stricture there was an opening in the rectum 1.5 to 2 cm. in diameter.

Pathologic Diagnosis: (1) Generalized peritonitis, (2) rectal stricture, (3) rectovaginal fistula, (4) rupture of the rectum, and (5) static ulceration of the rectum.

The rectal wall proximal to a stricture does not long retain its integrity. The constant damming of feces with the subsequent pressure upon the rectum leads to static ulceration. Areas of such ulceration will not stand undue stress. In the case herein described, the pressure exerted by the fetus as it passed through the birth canal was sufficient to cause rupture of the rectum.

Some months previous to the occurrence of this accident a similar case was admitted to the service. Rectovaginal fistula, and rectal stricture were present. Approximately fourteen hours following an instrumental delivery, the patient died. With the knowledge obtained from the above necropsy findings, one might readily deduce the occurrence of the same events in the case mentioned.

Rectal stricture and consequent static ulceration of the rectum present a grave obstetric problem. Cesarean section, sparing the birth canal and its neighboring organs the stress of labor, may be the key to its solution.

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1055 MORRIS AVENUE

SEPTATE VAGINA COMPLICATING LABOR

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CONGENITAL malformations of the female reproductive apparatus are usually of sufficient rarity in themselves to command attention, but more so when such anomalies are complicated by a full-term pregnancy. These have an incidence of less than 2 per cent of gynecologic pathology, according to Miller, the most common being the bicornuate uterus with a single cervix (Levison). In this connection one is reminded of a most interesting case of a viable fetus presented by Green and Miller, as an instance of a double vagina, cervix, and uterus. The present report is of a pregnancy complicated by a deformity of the vagina only, which, considering the embryology, is somewhat singular.

Mrs. W. M. A., aged twenty-seven, negro, gravida i, para 0; first came under my observation March 7, 1935, for prenatal care in one of the maternity clinics of the Chicago Health Department.

In a routine vaginal examination the anomaly, presently to be described, was first noted.

Menses began at eleven years, and were normal. Last period Nov. 18, 1934.

This was her first pregnancy, notwithstanding the fact that she had been married eight years and did not use contraceptives.

Her past personal and family history were unimportant. Laboratory tests of blood and urine remained negative and blood pressure within normal limits.

Physical examination revealed an apparently robust looking female of moderate muscular development, 119 pounds in weight and 5 feet 1 inch in height. With exception of the usual changes found in an eighteen weeks' pregnancy, nothing of an abnormal nature was observed until the vagina was examined.

The mons pubis was normal in conformation and hair distribution. The skin and mucosa of the labia were normal except for the discoloration and edema incident to pregnancy. Vaginal discharge was not excessive in amount. The clitoris presented no abnormality.

The vulva was of the marital type, with thickened remnants of carunculae hymenales. Extending downward from the vestibule in the median line was a well-developed septum, connecting the anterior and posterior commissures below and dividing the vagina into two almost equal portions, except for an aperture along its upper attachment which would admit the examining finger. As pregnancy advanced this septum shared in the general hyperplasia of the neighboring parts and was from 2.5 cm. to 3 cm. thick at its anterior and posterior attachments and from 1.5 cm. to 2 cm. in the mid-section, becoming thinner along its upper border (Fig. 1, *C*).

It was quite apparent that both sides of the vagina had been used for coitus, the opening upon the right being somewhat relaxed; whereas the left would admit two fingers with difficulty during the second trimester of pregnancy.

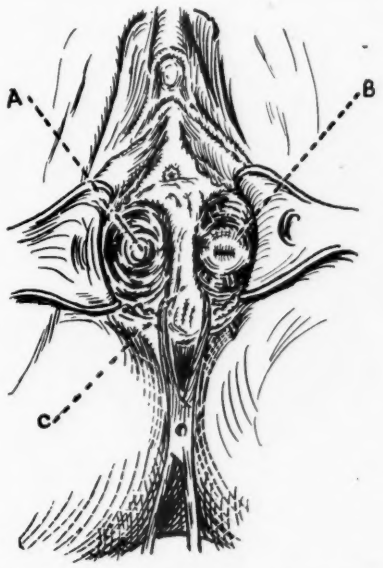

Fig. 1.—Incomplete vaginal septum complicating term pregnancy, in presence of normal fundus and single cervix.

The cervix was bulbous, of nulliparous type, discolored and presented in the left vaginal cleft (Fig. 1, *B*), while the right appeared almost as a blind pouch.

The fundus was slightly dextrose but presented no signs of deformity upon palpation. Early in the third trimester the fetus assumed the position of O.L.D. and remained so until the onset of labor.

Mensuration revealed the following: Interspinous diameter 26 cm., intercristate 27 cm., ext. conj. 18 cm., diagonal conjugate 10.5 cm., and transverse of outlet 8.5 cm. and suggested the moderately contracted, flat type of pelvis; and a prognosis of a complicated outlook for labor with operative indications was made.

The patient went into labor Aug. 31, 1935, and was admitted on the Obstetric Service of Provident Hospital. Progress was slow from the outset because of the contracted bony parts, deformed vaginal outlet and the time required for a rotation from left posterior position to an anterior. Pains were weak and infrequent and dilatation of the anterior lip was retarded. Near the end of the first stage it

was considered advisable to remove the vaginal septum under nitrous oxide anesthesia. The thickened, frontal portion was clamped with dressing forceps, excised and ligated with No. 2 forty-day chromic catgut. This was repeated at the caudal attachment, where considerable hemorrhage was encountered. Because of the danger of further aggravating this condition, the patient was allowed to recover from the effects of the anesthetic before the delivery was accelerated by oxytocic drugs. The first stage required sixty-three hours.

The second stage progressed slowly because of the acuteness of the pubic angle and because the parietals were arrested at the ischial spines. Under general anesthesia a deep left lateral episiotomy was done and the fetus extracted with low forceps.

The third stage presented nothing unusual.

The baby was female, weighing 3,250 gm. and required alpha-lobelin injection and oxygen stimulation for resuscitation. There was no appreciable injury from use of forceps and aside from an incidental hemorrhage from the cord, both baby and mother had an uneventful recovery.

COMMENT

A case is presented of a genital anomaly in a moderately contracted flat pelvis complicating a full-term pregnancy and resulting in dystocia. It is a point of interest whether or not the accidental use of the left vaginal compartment, in which the cervix presented contributed materially to the sterility during the eight previous years of married life. The operative correction of this deformity would have been advisable before labor.

309 East Forty-seventh Street

FIBROMYOMA OF THE CERVIX UTERI; THREE CASES, ONE DEVELOPING IN THE CERVICAL STUMP AFTER HYSTERECTOMY

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In the July, 1935, issue of The American Journal of Obstetrics and Gynecology, Counseller and Collins review the literature on fibromyomas of the cervix uteri. They emphasize the infrequency of cervical fibroids, especially large ones, and report a case of their own. I should like briefly to report three cases, one of which developed in the cervical stump after supracervical hysterectomy. I demonstrated the first specimen before the Chicago Gynecological Society on Nov. 15, 1929.

Case 1.—This was described in a report made at a meeting of the Chicago Gynecological Society and published in a previous issue of the Journal (19: 860, 1930). The illustration of the specimen (Fig. 1) was not included at that time.

Case 2.—Mrs. M. W. (No. 1316770), aged forty-three, was admitted to the Cook County Hospital on Oct. 13, 1932, complaining of a large swelling of the abdomen which she had noticed for about a year. Her general health had been good until the preceding year. The past history was negative except that the patient had had a supracervical hysterectomy in 1915 since which time no menstrual bleeding occurred. The general examination was negative except for a mild hypertension and moderate obesity. Abdominal examination revealed the presence of a symmetrically enlarged hard mass which extended upward almost to the xiphoid. There was a long, wide midline scar. On bimanual examination the cervix was found to be very

short, slightly softened, irregular, and over to the right side of the vaginal vault. The large mass felt abdominally was fixed in the pelvis and was stony hard. The diagnosis made was "solid tumor of an ovary." At operation on October 15, the mass proved to be one large fibroid arising from the cervical stump. In order to shell the fibroid out of the pelvis, an incision was made in what was taken to be the peritoneal covering of the fibroid posteriorly, way down low near the uterosacral ligaments. What was believed to be peritoneum proved to be bladder. Apparently the operator who had performed the supracervical hysterectomy had sewed the peritoneum of the bladder to the posterior surface of the cervical stump. As the fibroid grew up out of the cervix, the bladder retained its relationship and stretched upward and outward to cover completely the fibroid, not only anteriorly but also

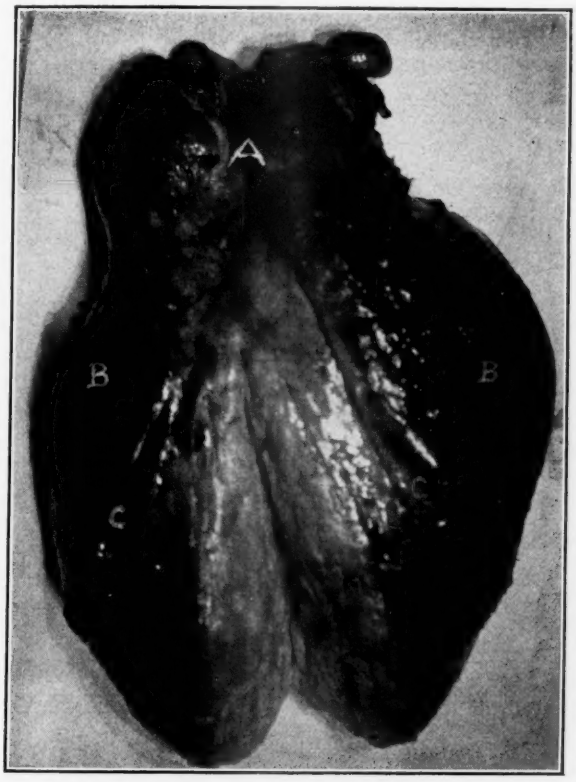

Fig. 1.—Photograph showing large cervical fibroid and small uterus on top. *A*, Body of uterus; *B*, fibroid of cervix; *C*, vaginal wall.

posteriorly. The rent in the bladder was easily closed. The bladder was then separated from the tumor. This was accomplished with some difficulty because of the extensive vascular connections between the bladder and the fibroid. The bladder when freed from the fibroid resembled a huge flat pouch. During the dissection, the right ureter, which was considerably distorted and dilated, was exposed on its medial aspect for quite a distance. However, since its lateral relationships were maintained, it was felt that its blood supply was ample to retain its integrity. A free piece of omentum was used to cover the exposed part of this ureter. After removal of the tumor and the cervix, a drain was placed near the exposed right ureter and another in the culdesac. The abdomen was closed as usual and a retention catheter was placed in the bladder. The fibroid measured 18 by 15 by 11 cm. (7¼

by 6 by 4½ inches). The patient had a febrile convalescence and an infected abdominal wound. However, she left the hospital in excellent condition thirty-three days after the operation.

CASE 3.—Mrs. S. G. (No. 1533201), aged thirty-four, was admitted to the Cook County Hospital on Oct. 5, 1935, complaining of a feeling of heaviness in the lower abdomen, a vaginal discharge, backache, and frequency of urination. The patient had had one full-term pregnancy and four miscarriages, and her menstrual history was not unusual. The past and surgical histories were negative and the general physical examination presented no abnormalities. Abdominal examination revealed a large, hard, movable mass approximately 15 cm. (6 inches) in diameter. Vaginal examination showed a marital outlet without any relaxation, and a smooth, firm but short cervix. The corpus of the uterus seemed to merge with the mass felt abdominally. The adnexa could not be felt. The diagnosis made was "fibroid uterus." An operation was performed on October 8, and it was found that the large mass was a fibroid of the cervix with the body of the uterus resting above it as in the first case. The fibroid and the corpus of the uterus were removed in one piece. The patient made an uneventful recovery and left the hospital ten days after operation.

55 EAST WASHINGTON STREET

INTERSTITIAL PREGNANCY

FRANK C. SPENCER, M.D., HONOLULU, HAWAII

MRS. K. M., a Japanese female, aged thirty-three, was first seen March 19, 1933. She complained chiefly of irregular menstruation and dysmenorrhea. A laparotomy had been done thirteen years before, appendectomy being apparently the only thing done at that time. She had one child twelve years old, and there had been no pregnancies since. Pelvic examination revealed a large cyst of the left ovary about the size of a baseball. General examination was negative. The Wassermann and Kahn reactions were negative.

Laparotomy was done at the Queen's Hospital March 24, 1933. Massive hydrops of the left tube coalescing with a large cystic left ovary was found. The right tube and ovary were grossly normal. A left salpingo-oophorectomy was done, and the patient made an uneventful recovery.

On March 19, 1935, the patient came into the office, complaining of nausea. Her last menstrual period was in January, and she had been regular previous to that time. Pelvic examination revealed a uterus two months pregnant. Irregular enlargement, especially on the right side, was noted.

On April 13 pelvic examination was repeated, at which time it was noted that there was unusual enlargement of the right cornu. She was still quite nauseated; urine examination was negative; weight was 101 pounds. The patient had no complaints except nausea. One cubic centimeter of eschatin (adrenal cortex hormone) was given hypodermically for the nausea.

On April 22 she again reported, stating that she had been free from nausea for three days after her last visit but it had returned. At that time she complained of slight pain in the right lower quadrant, and the uterus was irregular in outline, extending higher in the abdomen on the right side. The eschatrin was repeated for the nausea. She was seen again April 26, 27, and 28; the nausea had improved.

On May 7 the weight was 100 pounds, temperature 99.2° F., and the urine showed a very faint trace of albumin. By this time it was obvious that this was not a normally implanted pregnancy. The uterus had a sort of dumb-bell contour and extended almost to the umbilicus on the right side, where there were pain and tenderness. The patient was sent to Queen's Hospital for observation.

The next morning there was an increase in the size of the lower abdomen accompanied by increased pain and tenderness. The pulse was 104, temperature 98° F., respiration 24, and the R.B.C. 2,600,000 with hemoglobin of 50 per cent. The presence of internal hemorrhage was apparent and the diagnosis of interstitial pregnancy was concluded. One thousand cubic centimeters of 5 per cent glucose saline solution were given by vein. Later she was given a transfusion of 500 c.c. of citrated blood, and was operated upon.

A low midline incision was made and the abdomen was found to be filled with clots and liquid blood. It was estimated that there was about 1,000 to 1,500 c.c. of escaped blood in the peritoneal cavity.

A large mass about the size of a doubled fist was projecting from the right cornu of the uterus. It had a corrugated feel, was under tension, and there was no evidence of frank rupture. The mass was ruptured in manipulation and a four months' fetus and placenta were expelled. The right tube and ovary were of normal appearance.

A subtotal hysterectomy was done as rapidly as possible and such blood and clots as came into the field of operation were removed. The abdomen was closed without drainage; 1,000 c.c. of normal saline were given per rectum, and the patient was returned to her room. After an additional 1,000 c.c. of 10 per cent glucose were given by vein, the patient had a rather severe chill. Further convalescence was uneventful.

In this case, as in most cases of interstitial pregnancy, there was a complete amenorrhea. This amenorrhea is due to the fact that the fetus is in an environment more like that in normal pregnancy, and can therefore survive for a longer time than if it were located in the tube. The stroma of the uterine mucous membrane, because of its greater thickness, is able to form a decidua which can harbor the ovum and, at the same time, protect the muscle of the uterus from the corrosive action of the trophoblast. In the tube the connective tissue stroma is scanty and a true decidua cannot be formed, consequently the pregnancy will erode the wall and rupture earlier.

The mortality associated with interstitial pregnancy is high because of the sudden massive hemorrhage which may take place. Fortunately only 1 to 3 per cent of ectopic pregnancies are of the interstitial type.

This case is of interest because of its comparative rarity, the duration of the pregnancy and the apparent value of adrenal cortex hormone in the control of nausea and vomiting of pregnancy.

65-66 Young Building

Ohlin, C. A.: The Duration of Life of Spermatozoa in the Human Fallopian Tube, Acta Obst. et Gynec. Scandinav. **15**: 50, 1935.

In order to determine whether the epithelium of the uterine tube and its secretions in man may have any influence upon the duration of the life of spermatozoa, Ohlin performed experiments in vitro. He compared the duration of life of spermatozoa alone with spermatozoa mixed with epithelium removed from fresh, normal, fallopian tubes. He failed to find any difference in these two groups. The results, therefore, indicate that tubal epithelium and its secretions constitute a medium which is indifferent to the vitality and longevity of spermatozoa. The author believes his experiments support the modern theory of the short life of spermatozoa.

J. P. Greenhill.

COMPLETE TORSION OF TUBE AND OVARY COMPLICATING PREGNANCY

DEAN SHELDON, M.D., SANDUSKY, OHIO

COMPLETE torsion of the tube and ovary complicating pregnancy is a relatively rare condition and is very difficult to diagnose. Careful search of gynecologic and obstetric publications, as well as current textbooks, provides very little information on the subject. Corporeal movements and peristalsis are given by most authors as probable causes of torsion of the tube and ovary as seen in the nonpregnant state. When accompanying pregnancy it has been suggested that an abnormally large corpus luteum may precipitate the condition.

The symptoms are generally acute abdominal pain, tenderness and rigidity, occasionally accompanied by vomiting and elevation of temperature. A well-marked chemical peritonitis may follow the extravasation of blood into the peritoneal cavity. The severity of the symptoms is generally dependent upon the degree of torsion and amount of interference with the blood supply of the affected organs. Depending upon the location of the tumor, vesical and rectal symptoms may be well marked.

The pathologic changes are due almost entirely to a sudden interference with blood supply. This circulatory disturbance first manifests itself by a hyperemia, later by edema, and finally by gangrene with an entire obliteration of structure.

Mrs. H. L., twenty-nine years of age, para ii, was first seen in consultation on the afternoon of Dec. 12, 1934. Three days before, the patient had developed sudden excruciating pain in the right lower quadrant. The pain was only partially relieved by large doses of morphine. The patient at that time thought that she was about six weeks pregnant. The following morning blood tinged urine was passed, and a diagnosis of urethral calculus was made by the family physician. The pain had subsided in part in the afternoon that the patient was seen in consultation. There was no temperature elevation but a slight increase in the pulse rate. There was no vaginal bleeding.

Upon examination the abdomen was slightly distended throughout, with marked tenderness and muscle spasm over the right lower quadrant. Pelvic examination revealed a large tender mass in the culdesac. The cervix was displaced anteriorly, but because of the marked tenderness the body of the uterus could not be definitely outlined. In spite of a rather atypical history, a diagnosis of ruptured tubal pregnancy was made.

An exploratory laparotomy was performed. When the peritoneum was incised, a large amount of blood tinged fluid escaped. The right tube and ovary had undergone complete torsion and were gangrenous. The uterus was enlarged to the size of a six to eight weeks' pregnancy. There was no evidence of a corpus luteum of pregnancy in the uninvolved ovary. The right tube and ovary were removed and the abdomen closed without drainage. On the third postoperative day the patient aborted, otherwise the convalescence was uneventful.

Pathologic Diagnosis.—The specimen consisted of two fragments of what appeared to be blood clot. Diffusely hemorrhagic and no structural details could be identified.

Microscopic Examination.—The outlines of many greatly dilated vessels can be made out, but other than these shadowy outlines diffuse hemorrhage and necrosis prevent recognition either of the nature of the tissue or the process by which it was destroyed.

Diagnosis.—Hemorrhagic necrosis of unidentifiable tissue.

BLISS BUILDING

OBSTETRIC EFFIGIES OF THE MOUND BUILDERS OF EASTERN ARKANSAS*

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WE HAVE had the opportunity to study and to photograph four earthen vessels (two of them ours) which were exhumed with burial remains from the Mound Builder district of eastern Arkansas. The first of these effigies (Fig. 1) represents

Fig. 1. Fig. 2. Fig. 3.

Fig. 4.

a pregnant woman, with large abdomen and prominent breasts, in the erect-kneeling posture with her own hands applied to her abdomen. The second of the effigies (Fig. 2) represents a pregnant woman, with large abdomen, in the squatting knee-

*Submitted for publication, November 11, 1935.

chest position with her hands on her knees or thighs. If there were any doubt about the meaning of this effigy it would be immediately dispelled on looking at Fig. 3 in which the effigy has been tipped backward and the large protruding vulva exposed.

The third effigy of this series was not photographed; it was broken during an argument between two "dealers" over its price. This effigy depicted the end of second-stage labor. It was an exact reproduction of the earthen pot in Fig. 2, except that the infant's head had been delivered and the infant was being held in its mother's own hands. Mr. Drake, head of the Art Studio of the Mayo Clinic, has beautifully portrayed the likeness of this third effigy for us, and it is shown in Fig. 4.

The erect-kneeling posture (Fig. 2) with the knees somewhat separated and the hands resting on the thighs, is precisely the same as that assumed by the Mongolians, and probably also by the Yumas, when in labor. It can quite likely be said that the mythical Mound Builders, be they predecessors of our Indians or tribes of the same stock, were delivered of or delivered their young in the same position as many of the red squaws were known to have done in Colonial times. We cannot take the testimony of these vessels, the indelible records of an extinct people, as indicating the exact positions assumed during labor; they were effigies which depicted ideals.

PRIMARY TUBERCULOSIS OF THE VAGINA*

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(From the Obstetrical and Gynecological Service of the Kings County Hospital)

MRS. C. C. (Hospital No. 14171), aged thirty-nine, colored, married, born in United States. Admitted to Kings County Hospital April 23, 1935, complaining of (1) dispareunia, (2) vaginal discharge, and (3) moderate menorrhagia; all for the period of the past five years.

Tuberculosis in her family was denied; or contact with tuberculous persons. Husband living and well and denied tuberculosis in his family. Patient otherwise in excellent health.

Menstruation started at fourteen years of age; duration four days, interval twenty-eight days; always regular and not painful; menorrhagia started about five years before admission; last period March 30, 1935. Since marriage, a cleansing douche was employed after each period.

Obstetric history: Gravida xi, para ii, antepartum, intrapartum and postpartum periods were normal; both children are living and well; the youngest is nineteen years of age; contraceptives have never been employed.

Surgical history: No operations.

Physical examination in general negative.

Pelvic examination showed a multiparous outlet, perineum in good condition; no inflammation of the meatus or gland ducts. The vaginal mucosa had three strips (1.5-2.0 cm. in width) of granulomatous ulceration involving both lateral and posterior walls and extending from the fornices to the hymenal caruncles; surface covered with mucopurulent material, easily removed; edges smooth; inflammatory zone about the edges; bled readily on palpation and was sensitive to touch. Cervix pointed in the vaginal axis; freely movable; motion not painful; small bilateral

*Presented at a meeting of the Brooklyn Gynecological Society, October 4, 1935.

lacerations; otherwise appeared normal to ocular inspection. Uterus, normal in size, position, and motility; consistence normal. Fornices, adnexa palpable but not tender; culdesac clear.

Extremities: No adenopathy.

Admission diagnosis: Vaginal ulceration of tuberculous or syphilitic origin.

X-ray: Chest, no pleural or pulmonary pathology. Gastrointestinal tract, no intrinsic lesion of stomach or first part of duodenum; normal gastric motility after six hours. Barium enema, cecum and terminal ilium normal; appendix visualized and appeared to be normal; colon, no intrinsic lesion.

Cystoscopy examination: Examination of the bladder entirely negative. Pyelograms normal throughout. Bladder urine culture showed gas and gram-negative bacilli resembling *B. coli.* Kidneys (R. & L.) 2 or 3 white and red blood cells per high-power field; culture sterile; Pappenheim's stain on centrifuged sediments of bladder and kidneys showed no acid-fast bacilli.

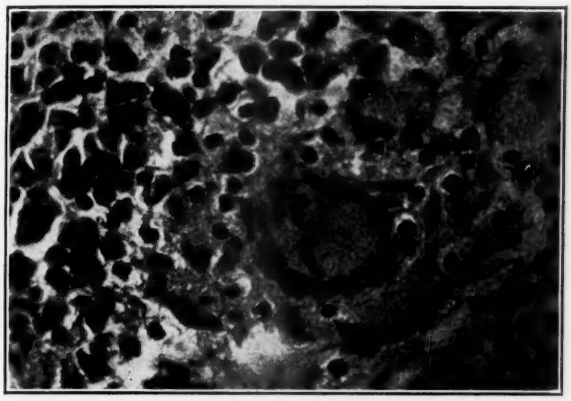

Fig. 1.

Guinea pig inoculation of urine was negative.

Biopsy specimen taken from the edge of one of the ulcerating areas in the vagina showed an area of ulceration; mucosa was replaced by cellular exudate consisting of small, round, and plasma cells; in the submucous tissue there were more or less isolated nodules composed of small, round, and endothelial cells; several of these contained typical Langerhans' giant cells suggesting that the process was of tuberculous character. Diagnosis: Tuberculosis of the vagina.

The patient was discharged May 4, 1935, and instructed to take douches of sodium bicarbonate (one tablespoonful to a quart of hot water) daily. On Sept. 24, 1935, the granulating areas had gradually epithelialized and were completely healed, being replaced by fibrous tissue; her pelvic examination was the same as previously described. Her complaints of dispareunia and vaginal discharge had been corrected but moderate menorrhagia still existed.

55 EIGHTH AVENUE

FATAL CASE OF YEAST MENINGITIS IN PREGNANCY*

HARRIS J. TIMERMAN, M.D., CHICAGO, ILL.

(*From the Chicago Maternity Center*)

MRS. C., aged thirty-four, gravida x, para v, received prenatal care at the Chicago Maternity Center from May 15, 1935, to June, 1935. Her last menstrual period was Oct. 1, 1934. She was classified as a Class I cardiac, with mitral stenosis. The Wassermann was negative.

This woman was first seen in her home on June 27, 1935, at which time she was eight and one-half months pregnant and not in labor. The patient gave a history of an acute upper respiratory infection of two weeks' duration with headache, nausea and vomiting, and dizziness. Normal temperature, pulse, and blood pressure. The only treatment instituted was supportive. On July 1, 1935, she lapsed into an intermittent coma. The headache and vomiting became severe. The findings at that time were marked dehydration, irrationality, exaggerated reflexes, slight neck rigidity and a positive Kernig's sign. Temperature 99.4°; pulse 84; blood pressure 94/44. The urine showed albumin 0, sugar 0 and diacetic acid ++. Obstetric findings were: Near term pregnancy, O.L.T, fetal heart 140, patient not in labor. She was sent to the Michael Reese Hospital with a diagnosis of a probable tuberculous meningitis and dehydration acidosis.

At the hospital the patient became worse rapidly, all of the meningeal signs increasing, and she died July 6, 1935. A postmortem cesarean section was performed, but the 6¼ pound baby died two hours later.

The pathologic diagnosis after autopsy was of a chronic leptomeningitis produced by *Torula histolytica,* with terminal bronchopneumonia. An acute verrucous endocarditis of the mitral valve was superimposed on an old healed endocarditis. Ascending pyelonephritis with multiple abscesses of both kidneys was also present.

Grossly the arachnoid of the brain was studded with whitish nodules measuring up to 3 mm. in diameter. Microscopic section of these nodules showed a marked infiltration of lymphocytes and in addition many large round or oval cells 16 to 20 micra in diameter. These cells had an eosinophilic cytoplasm with a highly refractile cellular membrane and from one to six nuclei approximating the size of a lymphocyte.

Yeast organisms were recovered from the lungs, but from no other organs. No similar organisms were found in the fetus.

*Read before the Chicago Gynecological Society, October 18, 1935.